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ACUTE POLIOMYELITIS AS A PRIMARY DISEASE OF THE CENTRAL NERVOUS SYSTEM

A Reconsideration of the Pathology, Symptomatology and Treatment, Based on the Hypothesis of Axonal Propagation of the Infective Agent

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INTRODUCTION

No acute infectious disease has been studied with greater intensity in its various aspects than acute anterior poliomyelitis and yet, despite the impressive body of data that has accumulated, a serious degree of confusion remains present in regard to its pathogenesis, its route of entry into the central nervous system, its mode of propagation and the reasons for its curious predilection for the anterior horns of the spinal cord For over twenty years, it has been possible to reproduce the disease in all its essential features at will in experimental animals and the conditions of such reproduction and the effects of the disease in them are known with satisfactory clearness in many details The

general nature and characteristics of the virus and its distribution in the tissues, even in man, are also known fairly well The confusion referred to largely concerns the application of the laboratory work to the interpretation of the pathology and clinical symptomatology in man, and particularly the widely accepted assumption that in its earlier hours there is, preceding invasion of the central nervous system, a period of "systemic," or "general," extranervous infection, which makes poliomyelitis comparable to various other "general" infections, such as typhoid fever and influenza The assumption was made by such important early students of the disease as Wickman (104) and Harbitz and Scheel (50), but it was not until the strong advocacy and elaboration of the hypothesis by Peabody, Draper and Dochez (86) in the Rockefeller Monograph on poliomyelitis and a few years later by Draper in his "Acute Poliomyelitis" (19) that it became established in the minds of the medical profession as a basic feature of the development of the disease, strongly coloring opinion on such vital points as the epidemiology, early diagnosis, prognosis and treatment For example, it has led to the belief that poliomyelitis need not affect the central nervous system at all, that the so-called abortive or masked cases are indistinguishable from common, minor infections of other kinds, that the appearance of the so-called meningeal signs (stiff neck, Kernig sign, etc) marks the moment when invasion of the central nervous system occurs, that treatment given before this time may prevent any invasion of the central nervous system, and that treatment so given offers the chief, perhaps the only, hope of benefit Draper, indeed, in the introduction to his book went so far as to say "It is designed to develop the idea that acute poliomyelitis is a general infectious disease, in the course of which paralysis is but an accidental and incidental occurrence " This idea, apparently still held by Draper (20), and perhaps generally, involves the assumption of a particular mechanism by which the virus of the disease reaches the central nervous system from "systemic" sources It will be of interest to consider the basis of this hypothesis of initial "systemic" infection, and of the hypothesis which is now supplanting it

"Systemic" propagation

Wickman (104) postulated a spread by way of the "lymphatics " By this term he apparently meant the perivascular spaces of Virchow-

Robin, without perhaps appreciating the fact—since then more fully studied (Weed (102), Dandy and Blackfan (17))—that the communications between the lymphatics of the body and their analogues in the central nervous system are so slight as to make them essentially independent systems Harbitz and Scheel (50) called attention to the difficulty in explaining the far-flung simultaneous lesions in the central nervous system by spread through the relatively short "lymphatic" spaces They say·

> Attractive as this theory may be, it is not, however, entirely adequate, we should have to expect a relatively patent and communicating path of infection along the vessel sheaths in the entire length of the spinal cord We know, however, that the arteries are end-arteries and their vessel sheaths, therefore, do not communicate The capillary vessels, on the other hand, form an interconnected network, but their sheaths must be regarded as too complicated a labyrinth for them to serve as a path of distribution for so rapidly traveling an inflammation, in any case propagation would have to take place in the sheaths of the veins, since these also anastomose, at least the larger branches But the longitudinal anastomoses are hardly abundantly enough present and, in especial, never attain, according to Kadyi, a very great length and in any case such a manner of propagation would not explain how the infiltration can accompany a peripheral arterial branch into the cord substance until it loses itself in the terminal branches and then disappear, as we have shown

Harbitz and Scheel submitted that it was "more natural to assume that the inflammation follows the surface and thence invades inwards", that the pia may be first affected anywhere, thence rapidly infect the entire cerebrospinal fluid, and so cause an infection of the entire nervous system through the communicating perivascular spaces The initial source of the infection is relatively unimportant, "whether from without through a lymphogenous channel, or hematogenously, or indirectly from a focus in the nervous substance "

This theory of spread through the subarachnoid space ("pial surface") obtained wide acceptance and, though in a much restricted sense, may be said still to hold today. Thus, Flexner (29) stated in 1912 that "the virus ascends by the nerves of smell to the brain, where it then multiplies in and about the olfactory lobes and, in time, passes, as I believe, into the cerebrospinal fluid which carries it to all parts of the nervous system " Experimental work has, since then,

given a certain amount of support to this hypothesis Virus has been occasionally, though quite exceptionally, found in the cerebrospinal fluid in animals inoculated intracerebrally, and it was established by Clark and Amoss (12) and frequently confirmed that direct inoculation into the subarachnoid space produces the disease, though with less regularity, than intracerebral inoculation (Flexner and Amoss (32)) It has even on occasions (Hurst (58)) been detected in the spinal fluid, comparatively late in the infection when little question of technical error existed However, the objections to this mode of propagation as the main or primary one are many and serious Perhaps, the strongest objection is the fact that virus has never been detected in human spinal fluid, despite many efforts made during the acute and early stages of the disease The validity of the occasional early detection of virus in the spinal fluid of animals intracerebrally inoculated has been seriously shaken by the observation by Fairbrother and Hurst (26) that without the greatest precautions the needle can easily reach the lateral ventricle, whence of course it will within a very short time appear in the subarachnoid space How rapidly this may occur was, curiously enough, indicated by the protocol of an experiment, some years previously, by Clark, Fraser and Amoss (13), who, placing a needle in the lumbar cistern, then made an intracerebral inoculation and recovered bloody, turbid fluid from the lumbar needle two and one-half minutes later While it has been shown that when virus is directly injected into the subarachnoid space it disappears within a comparatively short time (12), before the onset of symptoms, this is not positive evidence that the natural infection occurs by this route, but merely negative evidence, offering a possible explanation of the absence of virus in human spinal fluid at the time of active symptoms [1]

[1] Another argument against primary spread of poliomyelitic virus through the cerebrospinal fluid is the direction of flow in the subarachnoid space at the base of the brain This is from behind forward and upward In a recent case (personal observation) of epidemic meningitis, the relative amounts and density of the purulent deposits at different points in the subarachnoid space showed that the infection had probably entered through the cribriform plate below the olfactory bulb and had progressed forward and upward, along the anterior poles of the frontal lobes, in the longitudinal fissure anteriorly, and then backward and downward over the surfaces of the frontal, parietal and temporal lobes In poliomyelitis, on the contrary, as will be presently shown, the most anterior portions of the brain (frontal lobes) are rarely if ever involved, and the heaviest involvement is seen *posterior* to the olfactory bulbs at the base that is, in a direction opposite to that of the subarachnoid current

The thesis of initial blood stream invasion and secondary penetration of the meningo-choroid barrier has been so heavily emphasized by Draper and his followers, based on the experiments of Flexner and Amoss (31, 33), as a mechanism by which the initial "systemic" infection is converted into an infection of the nervous tissues proper that the grounds for it must be examined First, it postulates the occurrence in the human disease of a preliminary invasion of the blood stream, second it postulates an injury to the choroid plexus and vascular portions of the meninges, third, it postulates a general invasion of the nervous system through the injured vessels either directly or by way of the cerebrospinal fluid

In man, virus has never been demonstrated in the blood, nor in the monkey save briefly after large intravascular injections Invasion of the cerebrospinal fluid and nervous tissues is produced with the greatest possible difficulty by way of the blood stream The subject has been studied by Flexner and Amoss with great care, they found that the dosage necessary by this route is approximately 1250 times (31) that for direct nervous routes, and even then the incubation period was much delayed It was found (32) that when mild irritations were applied to the meninges, the dosage required was much less—about 50 times that for the direct nervous route This raised the question whether such an irritation might explain the entrance in man of virus from the blood stream into the central nervous system Flexner and Amoss's comments and conclusions here are of great interest They say (32)

> However, in certain instances, the lesions present not only resemble those caused by the intraneural modes of inoculation, but differ from them in the extent and degree to which the blood vessels, and especially those in the medulla and pons, are affected While the degree of perivascular infiltration does not afford a basis of discrimination, a sharp distinction may be drawn between the usual degree of vascular involvement, and the unusual extent in which it occurred in several cases of intravenous injection Vessels so greatly altered as those under consideration may be considered as contributing to the permeation of virus from the blood to the tissues . What appear, however, to be especially important are the changes detected in the choroid plexus, in which infiltrative lesions have hitherto not been observed the experiments indicate that when the poliomyelitic infec-

tion is induced by the intravenous injection of the virus, there arise, not only the common lesions of poliomyelitis, but also certain additional lesions of the blood vessels and choroid plexus which are of peculiar and distinctive nature

Since the precise mode of infection in human cases of poliomyelitis may be regarded still as an open question, this criterion of blood invasion may prove of assistance in the solution of the problem So far as can be judged from the study of the tissues from several human cases, a corresponding widespread vascular involvement would seem not to have occurred

Later on, in the same paper, they remark "The lesions in human cases of poliomyelitis would seem to correspond with those caused by intraneural and not by intravenous inoculation" And, finally "The experiments described support the view that infection in epidemic poliomyelitis in man is local and neural, and by way of the lymphatics, and not general and by way of the blood Hence they uphold the belief that the *infection atrium* is the upper respiratory mucous membrane" And in a later paper (33), the same authors say

The discovery of the main portals by which the virus enters the body has focussed attention on the conditions which favor or hinder its entrance Having reached the upper respiratory mucosa the virus may take either of two routes in invading the central nervous organs It may penetrate first into the local blood vessels and be carried into the circulation and thence to the nervous tissues, or it may pass into the lymphatic vessels surrounding the olfactory nerves and ascend more directly to the brain, medulla, and spinal cord

Experimental evidence suggests the latter route It is difficult to infect monkeys by way of the blood, and conversely, it is easier to infect them by way of the nasal mucosa It is the function of the choroid plexus and the pial lymphatic vessels to exclude the virus present in the blood from the nervous tissues When the virus enters directly from the nasal mucosa to the brain, the medulla and lastly the spinal cord become infected, from which it would appear that the virus entering the central nervous organs by way of the olfactory nerves permeates the organs continuously and is not distributed by the general circulation

It is evident therefore that the conclusions of Flexner and Amoss are really contrary to the deductions drawn from them and from clinical data by the proponents of the meningo choroid penetration theory

Their experiments demonstrated the importance and effectiveness of the barrier as a defensive mechanism, not that it is penetrated from the blood stream in the natural infection in man, and contradict the thesis of an initial blood stream infection

Axonal propagation

Most of the early experimenters were struck not only by the peculiar selectiveness of poliomyelitic virus for nervous tissue, but also by the ease with which animals could be infected by any method bringing it into direct connection with such tissue as compared with the difficulty of infecting by any other route, and, further, by the manner in which it followed peripheral nervous channels into areas of the central nervous system with which they were directly connected The possible routes of infection, however, seemed exhausted by the blood vessels and the lymphatics accompanying the nerves, and that a third alternative route—the nerve fiber itself (axis cylinder or myelin sheath)—existed, apparently failed to occur to any of them (save Romer (91)), even after (1917) Ransom (87) showed that tetanus toxin is conducted through "the protoplasma of the neurons" The perineural lymphatic pathway (mentioned in the quotation from Flexner and Amoss) was preferred by practically all the early workers Thus, Landsteiner and Levaditi (69) in their report of December 18, 1909, said that "Le virus peut se propager le long des nerfs pour atteindre le système nerveux central," as an inference from their experiments of inoculating virus into the right median nerve and obtaining primary paralysis of the right arm; but in a review of their experimental work about a year later, asserted their belief in ascent by the lymphatics, although noting the primary involvement of the nerve cells Leiner and von Wiesner (73) in the following year (1910), on the basis of similar experimental results from the inoculation of peripheral nerves came to the same conclusion, stating that "Die Verbreitung des Virus im Organismus scheint langs der Nerven, resp der dieselben begleitenden Lymphgefasse zu erfolgen"

Belonging to this same period are the remarkable observations of Romer (91), and it seems strange that they should not have suggested the alternative route mentioned, since they did suggest to him an inherent difficulty in the assumption of passage along the lym-

phatics and were certainly inconsonant with spread through the cerebrospinal fluid Romer says (p 99 et seq)

owing to the position of the operating table, we happened to make all our injections on the left side of the skull in the region of the central gyri

This situation corresponds with the fact that the lower limbs were affected first in most of our cases Paralysis appeared first in the left hind limb of only one monkey out of twenty which had been injected on the left side In eight cases one side was not affected before the other, but it must be remembered that at the time we were not paying attention to this point In no less than eleven experiments the limbs on the right side were paralyzed first In the majority of cases the paralysis began in the right hind limb When the fore limbs were affected first, it was the right one, with one exception, which was first affected Unfortunately, at the time when we became aware of the importance of this question we had almost finished our series of experiments I may mention, however, that both monkeys injected *ad hoc* on the right side became paralyzed first in the contralateral limbs Should these experiments be confirmed they would seem to indicate that the active agent spreads along the neuron or, at least, spreads more quickly in this direction than in any other It is to be supposed that in doing this it passes along the lymph channels accompanying the neuron, although this would pre-suppose a considerable degree of isolation of these channels

That long longitudinal "lymph channels" do not exist in the central nervous system had already been shown by Kadyi (21) and that perineural spaces could accompany a single group of nerve fibers for such a distance without communication with other drainage channels of the central nervous system was, indeed, a practical impossibility Certainly Romer's experiments, demonstrating the passage of virus through and along a definite nerve tract, the pyramidal, are susceptible of no other likely explanation than that of spread by way of the axis cylinders themselves, since even spread in the myelin sheaths would presumably lead to diffusion wider than that observed

Nevertheless it was not until some eighteen years later, in January, 1930, that axonal spread was seriously proposed and experimentally demonstrated This was in the report by Fairbrother and Hurst (26) of experiments in which after initial implantation in the brain and on the nasal mucosa the virus was shown to advance within the nerve

tissue itself, from the cerebral cortex to the thalamus, thence to the medulla and thence, with almost explosive suddenness, to the spinal cord It was shown that from its early or original site of implantation in the cortex, where conditions do not favor its survival, the virus tended to die out at a time when its effects on the lower centers of the nervous system were appearing, and, like Romer, they found evidence that the passage was along decussating channels They noted that virus was only exceptionally present in the cerebrospinal fluid, and concluded that this could be only a secondary or subsidiary route of spread when it occurred at all They also noted that nerve cell degenerations were antedecent to and often dissociated from the inflammatory reaction Finally they postulated, on the basis of their observations, that the anterior horn cells of the cord were more susceptible to the effects of the virus than other nerve cells They concluded that the virus travels chiefly by way of the axis cylinders

Confirmation of the truth of this revolutionary concept was supplied in June of the same year by Jungeblut and Spring (60) who transected the cord of a monkey at the level of the first lumbar vertebra, later inoculating a virus suspension in the brain, and finding (ninth day) thereafter typical lesions of poliomyelitis in the cervical and thoracic cord and a normal appearance in the lumbar cord below the point of transection, despite the fact that in the normal animal the lumbar cord is the site of predilection in the experimental disease Later in the same year Hurst (58) presented further evidence for the axonal theory Inoculating virus into the sciatic nerve, he not only found the earliest lesions in the corresponding portions of the lumbar cord (as had been shown before by Landsteiner and Levaditi (69) Flexner and Lewis (41), and Leiner and von Wiesner (73)) but later detected both virus and lesions in the corresponding portion of the cerebral motor cortex, and a little later still in the cervical cord Hurst (58) again stated that virus can occasionally be detected in the cerebrospinal fluid, and that this "plays a subsidiary part in the dissemination of the virus" But "No theory of the pathogenesis in terms only of the cerebrospinal fluid can provide a reasonable explanation of these observations"

The full import of these observations and conclusions in relation to practically all the clinical problems of the disease has not as yet been

appreciated It is obvious that if the theory of axonal spread is correct, other theories are incorrect We need not postulate a preliminary period of "systemic" infection, nor that poliomyelitis is a "general infectious disease" at all, in the sense of being extranervous before it is intranervous

It is to the purpose of examining the pathology and symptomatology of the human disease in connection with the point of entry of the virus and with the anatomy and functions of the central nervous system to see how well the axonal theory harmonizes with the facts, to attempt a re-interpretation of the clinical disease in its light, and to discuss certain changes which it involves in our attitude to some of the problems still awaiting solution, that the present paper is devoted

I THE INFECTIVE AGENT

The fact appears to be well established today that the microorganism responsible for epidemic poliomyelitis is not only filterable but also far below the limits of visibility under the ordinary microscope, nor has its artificial cultivation been conclusively demonstrated There was good reason for a time to believe that the globoid bodies discovered, cultivated and studied by Flexner and Noguchi (47), and Amoss (1) were actually the causative agents of the disease They were found in and recovered by culture from specifically infected tissues, both of man and the monkey, the cultures reproduced the disease in as late as the twentieth generation Nevertheless, the globoid bodies were not found in highly infectious filtrates and Amoss failed to detect an immunological relationship between them and the true virus Amoss's (2) recent conclusion is "that the relationship of the globoid bodies to poliomyelitis remains unsolved"

The globoid bodies average about 0 2 μ (200 $\mu\mu$) in diameter Recent experiments by Clifton, Schultz and Gebhardt (15) show that the virus particles are not more than one-quarter (50 $\mu\mu$) of this diameter and may be as small as one eighth (25 $\mu\mu$) The extreme minuteness of the virus may have a bearing on its mode of propagation within the axons so small a body might conceivably pass even through the neurofibrils themselves

That streptococci have any etiological relationship to poliomyelitis appears to be thoroughly disproved

The periodic fluctuations in virulence noted by Flexner, Clark and Amoss, (38) and later by Flexner and Amoss (35) is probably not only of epidemiological but also of clinical importance, since the degree of infectivity must be one of the two factors (the other being the efficiency of the defenses of the host) which determine the clinical course and outcome of the individual case The point will be again discussed

Burnet and MacNamara (9), in Australia, have demonstrated the existence of different strains of virus incapable of affording cross-immunity in monkeys, a discovery of obvious epidemiological and clinical importance

II POINT OF ENTRY

While perhaps it cannot be said with absolute certainty that there is not more than one portal by which the virus enters the body in the natural infection in man, nor that even the exact portal at which it enters has been conclusively demonstrated, there is impressive evidence (34) in favor of the nasal mucosa and almost equally impressive evidence against other routes

Active virus has been detected in at least one instance (Taylor and Amoss (97)) in the nasal washings at or near the beginning of the incubation period in a child who had a known recent contact with a case of poliomyelitis and five days later herself came down with the disease A brother of this child, who may have just passed through a mild case of the disease, also had virus in the nasal washings Flexner, Clark and Fraser (40) in 1913 found virus in the pooled nasal washings of both parents of a child suffering from the disease Kling and Pettersson (65) found virus in the pooled washings of four members of a family in which the father had recently died of poliomyelitis This appears to exhaust the list of published reports of virus detected by correct methods in the nasal mucosa of contacts Taylor and Amoss's unique first case is of particular interest and significance in showing the location of the infective agent in the early part of the period of incubation

In patients dying or recently recovered from poliomyelitis, virus can frequently (34)—according to Amoss (2), constantly—be recovered from the nasopharynx (tonsils) As a rule, according to the experiments of Flexner and Amoss (34) it disappears rather soon, since it

could not be recovered from the tonsils surgically removed during convalescence They conclude that chronic carriage is at least exceptional Lucas and Osgood (78), however, found virus in the nasopharyngeal washings of a patient who some months before had suffered a second attack of the disease The studies of Kling, Wernstedt and Pettersson (66) of the nasopharyngeal washing of some 12 cases during various periods of convalescence unfortunately must be rejected as inconclusive

The detection of virus in the nasopharyngeal secretions and adjacent lymphoid tissues (tonsils and adenoids) in cases with the fully developed disease (Flexner and Clark (36), Landsteiner, Levaditi and Pastia (72), Thomsen (98), Flexner and Amoss (34)) does not, however, prove that this area is the site of entry, since Flexner and Lewis (43), Landsteiner, Levaditi and Danulesco (71), and Thomsen (98), showed that it is also the site of exit of virus from the central nervous system In monkeys experimentally inoculated by the intracranial route, virus was later discovered in the nose The fact has obvious importance in relation to the spread of the disease

Neither the clinical symptomatology nor the post mortem findings indicate the portal of entry While acute infections of the throat, such as acute follicular tonsillitis, have occasionally preceded poliomyelitis, they are so exceptional as to suggest—together with the generally accepted belief that this form of tonsillitis is due to streptococci—that the concurrence is accidental In most epidemics—there are occasional exceptions, such as the outbreak in Hesse-Nassau studied by Muller (82)—outspoken clinical evidence of upper respiratory inflammation have been conspicuously absent, at the onset or immediately before or after The same may be said of evidences of gastro enteritis Although in some outbreaks of poliomyelitis there has been a good deal of diarrhea, in the majority it has not been present in more than a small minority of cases Since both are diseases epidemic in the summer months and in young children it is not surprising that outbreaks of both should sometimes coincide

The post mortem pathology gives little direct support to the view that the disease penetrates either through the nasopharynx or through the gastrointestinal tract Harbitz and Scheel (50) minutely examined the nasopharyngeal mucosa in two cases without finding

abnormalities Various pathologists have examined the gastrointestinal tract and, while noting with varying frequency hyperplasia of the lymphoid structures (solitary follicles, Peyer's patches) have not found such changes with uniformity Moreover, this hyperplasia appears to be part of a hyperplasia of the entire lymphopoietic system of the body and not a local phenomenon or regularly related to gastroenteric disturbances

Reviewing the human evidence, it seems safe to say that, as a general rule, *the virus of poliomyelitis excites little if any inflammatory disturbance on or in the surface membranes of the body, that its entrance is, in the great majority of cases, at least, wholly silent*—facts which are doubtless due to its high degree of specificity for nervous tissue

For a solution of the problems of how and where the infective agent of poliomyelitis, once deposited on the body surfaces, is able to penetrate thus silently into the central nervous system, provided as it is with a special mechanism of defense against infection from the blood stream and possessing the slightest of communications with the lymphatic system, we must in the main depend upon the results of animal experiment

Reference has already been made to the conclusions of various workers that infection is accomplished with ease by any method bringing the virus into direct contact with nerve tissue and that it is readily conducted through the peripheral nerves into the central nervous system The problem would therefore appear to narrow down to the determination of places in the body where nerve endings are exposed at the body surface and to the detection by direct experiment at which of these—if more than one exists—infection can be produced, preferably without trauma

The mucous surfaces of the body are obviously the only ones to be seriously considered, and, of these, we may make three broad divisions the upper respiratory, the lower respiratory, and the gastrointestinal While Leiner and von Wiesner (73) reported successful inoculations by all three of these, other experimenters at the same period and later have been able to confirm their results only in the case of the first The gastrointestinal route has, indeed, been seriously considered from time to time by occasional students of the disease but the recent in-

vestigations of Clark, Roberts and Preston (14) appear to have finally disposed of its claims

Flexner and Lewis (44), Landsteiner and Levaditi (70) and Leiner and von Wiesner (73) all within a short space of time (1909–10) succeeded in infecting monkeys by the application of virus to the nasal mucous membrane In the first experiments the membrane was traumatized, but it was soon found that success could be obtained by simply swabbing infective material on the surface or by applying a cotton tampon to the uninjured surface Quite recently, Rhoads (89) reports almost uniform success from repeated dropping of virus suspensions in the nose [2] While, on the whole the method of nasal application gives less uniform results than intracerebral inoculation, it remains the only method by which experimental poliomyelitis can be produced without trauma, and from the body surface It is one of Flexner's most important contributions to our understanding of this disease that he first recognized the unique significance of this route of entry and has continued to study and emphasize its importance As early as 1912, in his Huxley lecture (28), he made his famous generalization "The large peripheral nerves are prevented anatomically from being infected in nature, while the small olfactory filaments are advantageously placed to act as the means of transportation Hence the view that the nasal mucous membrane is the site both of ingress and egress of the virus of poliomyelitis in man" This view he repeated in 1931 (30) in a brief note (Science) stating "The indications, then secured and since confirmed, are to the effect that the virus is nerve conducted, as it enters and even as it leaves the body of infected human beings and animals *via* the respiratory mucous membranes" Flexner's view, which has come to be generally accepted, therefore implies that the virus not only enters (and leaves) the body

[2] A recent personal communication from the Rockefeller Institute describes the method as consisting of washing fairly large amounts of virus suspension into the nose on successive days for about a week, using a number of different strains This illustrates that the difficulty apparently varies greatly from time to time due to factors which are still obscure Flexner and Amoss (107) suggest that one of these is the state of the mucous membrane itself, in some animals it is "effective" as a barrier, in others "ineffective" Another factor is doubtless the state ("virulence") of the virus itself In a recent series of experiments (p 100), Faber and Gebhardt, using a modification of technique devised by Schultz and Gebhardt (unpublished), had very few failures

through the upper respiratory mucous membrane, but at a particular area within it [3]

A brief résumé of the anatomy of the olfactory mucous membranes and nerves will show what extremely favorable—probably unique—conditions they present to the attack of a strictly neurotropic virus once lodged on the surface, even though it were wholly incapable of setting up any local inflammatory reaction in the sustentacular cells or other supporting tissues

As described by Parker (85), the olfactory portion of the nasal mucous membrane in man occupies an area of about 250 sq mm in the superior nasal meatus in each naris, on the septal and lateral walls Under normal conditions of quiet breathing the air currents do not reach to this height but are brought to it by more forcible inspiratory efforts (sniffing, etc) It is covered by a layer of mucus, which in man may or may not contain neutralizing substances for the virus of poliomyelitis (Amoss and Taylor (3)) *In and upon* (108) *this mucus, projecting from the epithelial surface, lie the free ends (olfactory hairs) of the processes (modified dendrites) of the olfactory cells. These are true ganglion cells whose axons ascend, without intervening synapsis, in the olfactory nerves (about 30 in man) through the cribriform plate of the ethmoid bone into the olfactory bulb* The olfactory axons are unmyelinated It is possible, although on the whole unlikely (in view of the established slightness, as shown by Weed and others, of communications in general between the subarachnoid spaces and the systemic lymphatics) that the lymphatics surrounding these nerves in their nasal portion are in natural communication with the subarachnoid space It is perhaps more likely that the barrier between the lymphatics and the subarachnoid space is rather easily broken down either by pathological increases of pressure from inside (as in the experiments of Key and Retzius (64)) or by acute inflammatory disease There is, however, no indication that communicating spaces exist along the nerves from the nasal mucosa *into* the olfactory bulb

[3] The experiments of Levaditi and Danulesco (75) beautifully demonstrate the limited area of susceptibility All of 9 monkeys in which virus was applied to the uninjured nasal mucosa (5 by tampon, 4 by simple swabbing) came down with typical poliomyelitis Both of 2 monkeys in which it was applied by rubbing to the pharynx (throat, tonsils) remained unaffected

The ideal condition existing in the peripheral area of the olfactory tracts for transmission from the body surface of an axonally propagated virus directly into the central nervous system is, therefore, manifest Such conditions are not duplicated elsewhere in the body The vital importance of the protection afforded by the overlying

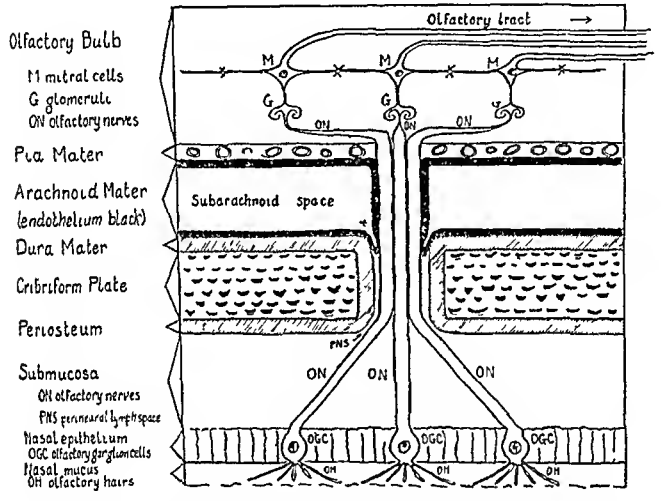

FIG 1 THE OLFACTORY MUCOUS MEMBRANE, THE OLFACTORY NERVES, THEIR CONNECTIONS AND ANATOMICAL REACTIONS

The immediate exposure of the terminal filaments (olfactory hairs) of the olfactory nerves to virus deposited in the nasal mucus is evident as well as the directness of the pathway, through the olfactory cell and axon, *into* the olfactory bulb, whence by passing the glomerular synapses, it is free to travel out from the bulb through the olfactory tract to the various connections in the interbrain, hippocampal formation of the neopallium, etc as explained in the text

The diagram also shows the subarachnoid as a closed space within a continuous lining membrane (the arachnoid mater) not in open communication with the extraneurous lymph spaces Virus or bacteria (such as the meningococcus) breaking through at the point marked "x" would invade the subarachnoid space but could only penetrate into the interior of the bulb or other parts of the nervous tissues proper after passing through the pial layer or through the perivascular spaces (not shown in the diagram), if such a process actually occurred, it should be more diffuse, and follow the upward and forward direction of the current of the cerebrospinal fluid along the frontal lobes and longitudinal fissure, instead of downward and backward along the base to the regions actually found to be mainly affected The agreement of the pathology and early symptomatology with the direct nervous route is discussed in the text

mucus on the surface is also evident since this and the state of the cell membranes appear to be the only effective immediate barriers to the entry of virus, once it has been implanted on the surface [4]

That virus actually ascends along these nerves *into* the olfactory bulb was shown by Landsteiner and Levaditi (70) in 1910, and again by Flexner and Clark (37) in 1912, who added the important observation that at the period—forty-eight hours after application to the nose—when it was found in the bulb it could be detected neither in the medulla nor in the spinal cord [5]

We may accept, without much hesitation, *the olfactory mucous membrane as the most probable route of penetration of the virus of poliomyelitis from the surface into the central nervous system, and it should be noted that it is quite unnecessary to assume in explanation of this penetration any preliminary local irritation or inflammation* nor, indeed, anything more than the absence of specific neutralizing substances in the superficial mucus, or than a change in the physico-chemical state of the surface membranes of the olfactory hairs in the direction of increased permeability

[4] The actual deposition of the infective material in the superior nasal meatus, to which the olfactory nerve endings are limited, must be rather direct Hilding (54) has shown that the surface currents created by the cilia of the nasal epithelium move particulate matter deposited on the surface downwards and backwards, and thus *away* from the superior meatus This mechanism doubtless has a certain protective value in the case of poliomyelitis

[5] Brief reference may be made here to experiments by Faber and Gebhardt that were in progress during the preparation of the present paper and are soon to appear in the Journal of Experimental Medicine Monkeys inoculated intranasally by the method referred to in footnote 2, were sacrificed on the third, fourth, fifth, sixth and seventh days thereafter, in all cases before paralysis On the fourth day, virus was detected in the olfactory bulb alone On the fifth day, it was found in the olfactory bulb, hypothalamus and medulla On the sixth day, it was detected again in these places and also in the thalamus and midbrain On the seventh day, for the first time, it was found in the spinal cord, both posteriorly and anteriorly, and in the intervertebral ganglia In none of the experiments was virus detected in the cerebral cortex (excepting the hippocampus, in small amounts on the seventh day) nor in the cerebellum

It is quite impossible to interpret the results except by propagation through the nerve tissues proper, apparently by a fairly well defined route within the central nervous system

The application of the results to the human disease appears to be reasonable since the same point of entry, the nasal mucosa, was used

III ANATOMICAL CONSIDERATIONS, NERVE TRACTS AND CONNECTIONS, BLOOD SUPPLY, PERIVASCULAR SPACES

Since this paper deals with the thesis of nerve conduction of virus along particular channels, it is appropriate to review certain aspects of the nervous anatomy at this point A brief discussion of the blood supply and of the channels of tissue drainage in the central nervous system is appended, as having a bearing on the discussion of certain disputed points

Olfactory mucosa and olfactory nerves

The anatomy of these structures has already been described under "Point of Entry"

Connecting pathways from olfactory bulb[6]

From the olfactory bulb the outgoing fibers pass on to the first relay in the olfactory lobe and thence, or from the next relay in the parolfactory lobe (rudimentary in man) in the anterior perforated space, the olfactory fibers, afferent and efferent, diverge along several different pathways, which later again converge The pattern of these is very complex in detail, but for present purposes may be sketched in its broader outlines

In primitive animals, the olfactory pathways pursue a basal course to the thalamic region, ending in relays with fibers leading to the midbrain, lower brainstem, and spinal cord The basal olfactory bundle of Wallenberg (described in Edinger) appears to be the remains of this primitive tract It terminates partly in the hypothalamic areas in or near the mamillary bodies, partly in the interpeduncular ganglion, and partly in lower areas of the brainstem as yet not known with certainty Some of the fibers, at least, in this tract have been shown by the method of degeneration to run an uninterrupted course from the olfactory bulb to the mamillary bodies From the last, a large tract, the bundle of Vicq d'Azyr, connects, by one of its divisions with the anterior nucleus of the thalamus and by the other with the dorsal tegmental nucleus of Gudden in the central gray matter of the midbrain This nucleus, which will again be referred to, is an important

[6] The data here summarized have been obtained mainly from Edinger (22), Tilney and Riley (99), and Huber and Crosby (56)

olfactory relay point for "the transference of impulses received by the olfactory portions of the brain to the bulb and spinal cord" (Tilney and Riley (99)) It is also connected with the interpeduncular nucleus, already mentioned, through the fasciculus retroflexus of Meynert, and with the habenular nucleus of the thalamus

With the evolution of the end-brain, new olfactory tracts have been formed circling about the thalamus, to reach, through various relays, the cortical areas of the limbic lobe, the chief of which are the hippocampus and its later outgrowth, the uncus From these cortical areas of smell, other tracts descend, mainly throughout the fornix to the mammillary bodies (hypothalamus), the thalamus (anterior nucleus, habenular nucleus) and thence, again, to Gudden's nucleus

The connections of this important structure with the lower centers, while not fully established in all respects, appears to be along two tracts chiefly the reticulo-bulbar-spinal, and the fasciculus of Schutz The former establishes connections with the visceral motor and secretory mechanisms of the medulla and cord, the latter is, according to Tilney and Riley, the remains of an ancient motor path connecting the olfactory centers with the anterior horns of the spinal cord

Finally, commissural connections exist between the various olfactory centers of the opposite sides Thus, the two olfactory bulbs are connected through the anterior commissure, while the hippocampal areas, the thalami, etc are similarly connected with their pairs

This already much condensed description of the olfactory radiations from the olfactory bulb may be summed up as follows

A From the olfactory bulb and lobe (anterior perforated gray substance) the chief pathways are

(1) To the hypothalamus and interpeduncular ganglion, thence to the thalamus (anterior and habenular nuclei) and midbrain (central gray matter adjoining the aqueduct of Sylvius),

(2) To the hippocampus (Ammon's horn), and thence to the same areas as in (1),

(3) To the olfactory bulb of the other side

B From the areas, above mentioned, in the interbrain and midbrain, connecting tracts extend to the medulla and spinal cord

Assuming that a neurotropic virus, once firmly implanted in the

olfactory bulb, were propagated along the outgoing olfactory tracts and established secondary loci of infection in the various relays of ganglion cells (nuclei) in these paths, we should look for evidences of such secondary infection particularly in the hypothalamus, thalamus, tegmental area of the midbrain (gray matter adjacent to the aqueduct), Ammon's horn, and olfactory bulb of the other side Inspection of necropsy protocols, particularly those of Harbitz and Scheel, does in fact show heavy involvement of some of these areas, particularly the hypothalamus, the thalamus (to a lesser degree) and the central gray of the midbrain Ammon's horn (referred to in the protocols as the inferior temporal gyri) was also affected to a greater extent and more constantly than other areas of the neopallium

At this point attention may be focussed on some of the functions of one of the most heavily involved areas, the hypothalamus The various nuclei in this portion of the paleothalamus appear to exercise a controlling or regulatory ("adjustor") function over the entire vegetative system of the body, both sympathetic and parasympathetic, and irritative disturbances originating in it display an extraordinary variety of corresponding manifestations, among them abnormalities of body temperature (fever, subnormal temperature), of sleep (drowsiness, insomnia, sleep reversal), of cardiac rhythm, of perspiration (excessive sweating), of bladder function, of gastrointestinal motor function, of metabolism As will be seen when the symptomatology of poliomyelitis is discussed, many of the very early clinical features of the disease belong to the category of vegetative hypothalamic disturbance A point of particular interest here is the recent discovery by Cushing that stimuli applied by injections into the infundibular (hypothalamic) portion of the third ventricle lead promptly to vomiting, the commonest onset symptom, after fever, of poliomyelitis

Connections between the spinal cord and brain

Efferent paths With exceptions to be mentioned—the chief of which is the pyramidal tract—most of these originate in the midbrain and cerebellum It is noteworthy that the great motor pathway, *the pyramidal*, originating in the precentral area of the cortex, is heavily myelinated and runs an uninterrupted course to its termina-

tions in the anterior horns of the spinal cord The point is of interest since Fairbrother and Hurst have shown how poorly adapted are the cortical areas to survival—and hence, presumably, natural implantation—of poliomyelitic virus It is therefore unlikely that this tract would become infected at its cortical end nor, since it is presumably protected by its myelin sheaths, that it is exposed to infection during its passage down to the anterior horns of the cord Further, neither the histopathology of poliomyelitis nor the early symptomatology gives evidence of conspicuous involvement of the motor cortex For these reasons, it is improbable that the natural route of infection is through the pyramidal tract

The *rubrospinal* tract is more nearly in line with the areas of secondary infection in the midbrain described in the preceding section The red nucleus in which this tract originates lies in the tegmentum of the midbrain not far from the nucleus of Gudden and extends down to the subthalamic region Its anatomical relationships are therefore such as to expose it to infection from presumptively infected areas in the olfactory system Its chief connections are, however, mainly with the corpus striatum and cerebellum, both far removed from the olfactory centers Its functions are motor (synergic and associated automatic control) and it descends directly to the anterior horns of the cord Whether this tract is in fact one of the main channels through which infection descends to the cord is not perhaps to be answered on purely anatomical grounds, but rather on clinical considerations and perhaps on future experimental study Involvement of the red nucleus in the inflammatory process appears to be exceptional The character of the symptoms in the preparalytic stage and the order of their appearance do not suggest that it is the main route of propagation of infection

The *tectospinal tract* originating in the tectum of the midbrain and passing down to the anterior horn cells is largely concerned with visual function, supplying a "defense mechanism for the protection of the eye by means of the upper extremity" In its origin it is separated from the olfactory centers and while the importance of its rôle in the dissemination of poliomyelitic infection, remains in part, like that of the rubrospinal tract, to be determined by the clinical evidence, it is clear that its anatomical distributions—largely to the

cervical cord—are not in accord with the usual manifestations of an infection characteristically involving the entire cord, particularly the lumbar regions Moreover, visual disturbances are exceptional in poliomyelitis

Our knowledge of the *reticular formation* of the midbrain, pons and medulla and of the *reticulobulbar* and *reticulospinal tracts* is as yet incomplete Reference has already been made to descending fibers in these tracts connected with Gudden's nucleus Hypothalamic connections have been traced from the nucleus tuberomamillaris (infundibulum) to the mamillary body and thence through the mamillotegmental fasciculus to the substantia reticularis of the central grey matter of the midbrain It appears that the cell groups in the hypothalamus (tuber cinereum, body of Luys) and in the formatio reticularis through the brainstem have important regulating or controlling functions over the various sympathetic and parasympathetic functions As Spiegel (110) remarks "Vegetative centers are found, therefore, in many levels of the central nervous system and not only in the segmental cells of origin of preganglionic fibers The activity of these cell groups is modified by that of the formatio reticularis of the rhombencephalon, of the hypothalamus, and of the forebrain" The cells of the formatio reticularis are connected with each other and with spinal centers by tracts that have not as yet been completely mapped Papez (109) has recently outlined one of them from the upper pons or lower midbrain to the medulla and cord Their particular interest to us is twofold first, they appear to be intimately connected with centers already described in the hypothalamus and midbrain closely adjacent to or in the direct pathway of the olfactory tracts, second, the formatio reticularis is repeatedly mentioned by Harbitz and Scheel as being frequently and rather heavily involved in the inflammatory process of poliomyelitis (see under "Distribution of Lesions")

For the sake of completeness, the *vestibulospinal* and *olivospinal* tracts, both originating in the medulla, may be mentioned The first of these, controlling equilibrium, runs from Deiter's nucleus to the anterior horn cells of the cord throughout its length There is, however, little or no pathological or clinical evidence of its involvement in the ordinary course of poliomyelitis and its importance as a route

of propagation of the infection is probably slight The same conclusion may be made concerning the olivospinal tract, which extends only to the upper cervical segments of the cord Finally, "an ancient olfactory motor pathway" is said to connect the anterior horns of the cord through the dorsal longitudinal fasciculus of Schutz with the dorsal tegmental nucleus of Gudden, already mentioned as an important synaptic point in the descending olfactory pathways The extent and even the functional integrity of this tract in man is, however, apparently somewhat in doubt and it may be rudimentary Since little or nothing is known of clinical disturbances that might be related to injury or irritation of it, the extent of its possible participation in the transmission of infection must be wholly conjectural

Taking the chief efferent tracts connecting the higher centers with the spinal cord into consideration as possible or probable routes of propagation of poliomyelitic infection from the olfactory centers to the anterior spinal horns, we may tentatively exclude the pyramidal, the tectospinal, the vestibulospinal and the olivospinal, we may consider the rubrospinal as a possible, though perhaps not a probable, route, and the reticulospinal as a more likely route, subject to further consideration Finally, we might regard the "ancient olfactory motor pathway" extending from the dorsal nucleus of Gudden to the anterior spinal horns as a probable route, were more known of its magnitude and functional capacities in man It may however, be vestigial

Afferent paths These may be divided into two groups, the sensory tracts, proper, and the cerebellar Both of the latter—the *ventral* and *dorsal spinocerebellar*—connect the gray matter of the cord, chiefly the columns of Clarke, with the cerebellum, the former through the inferior cerebellar peduncle and the latter through the superior cerebellar peduncle Since the cerebellum has been found to show only the slightest involvement in the pathological process of poliomyelitis and since cerebellar symptoms are conspicuously absent in the very early clinical phases of the disease, it is highly improbable that these tracts participate in the descent of the infection to the cord While it is true that the cells of Clarke's column are sometimes involved in the inflammatory process in the cord itself, there is reason to suppose that they become infected through other channels than those from the cerebellum

The two great sensory tracts—that of *Goll and Burdach*, and the *spinothalamic*—deserve closer attention The first of these originates in the dorsal root ganglia of the spinal cord, ascends to the medulla where, in the nuclei gracilis and cuneatus, its fibers have synapses with neurones that go through the mesial fillet to the lateral nuclei of the thalamus (neothalamus) This tract conducts impulses of somesthetic sensibility The spinothalamic tract, which conducts impulses of pain and temperature, originates in the posterior horns of the spinal cord (substantia gelatinosa of Rolando)—in relay with the dorsal root ganglion cells through the tract of Lissauer—and ascends directly by single neurones, for the greater part, to the lateral nuclei of the thalamus (neothalamus)

It will be seen that the thalamic terminals of both tracts are in the lateral nuclei of the thalamus, whereas the olfactory thalamic relay points are in the mesial portions of the thalamus (anterior nuclei, habenular nuclei), or paleothalamus The two portions of the thalamus are, however, undoubtedly interconnected by intercalary fibers Highly pertinent to the present discussion is Herrick's (52) summing-up of the functional interrelationships in this area He says "The diencephalon is a relatively neutral zone between the large olfactory centers above and the centers of visual and other types of sensibility below *Here the descending correlation tracts from the olfactory field meet the ascending fibers of all other sensory systems*" (Italics added)

As to which of the two great sensory tracts now under discussion is more probably implicated in the passage of infection downwards may now be discussed Infection descending from the thalamus through the mesial fillet would involve the gracile and cuneate nuclei in the medulla and might be expected to set up some disturbance of the sense of somesthetic discrimination In point of fact, these bulbar nuclei are much less involved in the inflammatory reaction, according to Harbitz and Scheel, than other portions of the medulla, nor have neurological disturbances suggestive of early involvement of the tract been described It therefore seems unlikely that this is one of the main routes of descending infection

On the other hand, *on infection traveling along the spinothalamic tract should lead to an inflammatory reaction in the posterior horns of*

the cord—and in the dorsal root ganglia through the tract of Lissauer—and to disturbances of pain and temperature These changes are, in fact, both usual and characteristic in poliomyelitis and will be discussed in greater detail in subsequent sections of this article

Intra- and intersegmental connections It is not, perhaps, always appreciated that the mass of neuronal fibers and connections connecting cells within segments or cells of adjacent segments is considerably greater than that of those connecting the cord with the higher intracranial controlling or modifying structures These intra- and intersegmental connections are of various sorts, which may be divided into two main groups those connecting spinal cells with one another, and those connecting the cells of the intervertebral ganglia with cells of the cord, and the connections may be either direct through axons with dendrites or cell body, or intermediate, through intercalated, connector neurons In the cord itself, such connections exist between cells of the same or of different classes (as, for instance, between different anterior horn cells, and between posterior horn and anterior horn cells), and are largely intrasegmental The cells of the intervertebral ganglia are connected (*a*) with the cells of the spinothalamic tract in the posterior horn (pain and temperature), (*b*) with the cells of the anterior horn (direct spinal reflex), (*c*) with the cells of the column of Clarke (synergic control), (*d*) with cells of the lateral horn (visceral—sympathetic—impulses and effects) Most of the fibers entering the cord from the spinal ganglia divide into ascending and descending branches and thus establish both intra- and intersegmental connections

In brief, the structural arrangements of the cord are such that an infection descending through the neurones of the long tracts connecting it with the intracranial portions of the central nervous system and attacking any of the spinal cells would have open channels to at least most of the others in the immediate neighborhood To a certain extent the spread of infection in a given segment would tend to be limited to that segment and its next neighbors according to the range of the connecting intra- and intersegmental and intercalary fibers, and perhaps a certain degree of one-sidedness might also result from similar limitations of distribution

It has already been suggested that one of the more probable routes of descent is through the spinothalamic tract In such a case, we should expect to find the infection lodging first in the cells of the posterior horns We should next expect it to reach the dorsal root ganglia through the tract of Lissauer From both these foci we should expect it to follow the connecting neurons (*a*) to other portions of the posterior horns, (*b*) to the columns of Clarke, (*c*) to the cells of the lateral horns, (*d*) to the anterior horn cells—all more or less simultaneously The first spinal symptoms, by this hypothesis, should be due to disturbance of the posterior horn cells, chiefly in the field of pain and thermic sensibility Next, we should find disturbances due to involvement of the cells of Clarke's column (interference with synergic control, ataxia), splanchnic disturbances from the lateral horns, and disturbances due to involvement of the anterior horn cells (increased irritability with hyperactive reflexes followed by flaccid paralysis) The extent to which such expectations are corroborated by available facts will be presently discussed

Summary The anatomy of the tracts of the central nervous system has been reviewed in relation to the hypothesis that the virus of poliomyelitis enters the body through the olfactory cells of the nasal mucosa and is propagated from that point through the olfactory tracts and their principal connections to reach its usual ultimate goal, the anterior horns of the spinal cord The distribution of lesions, the experimental and clinical evidence (separately discussed in greater detail) considered in conjunction with the various neural pathways particularly exposed to infection indicate that the virus first reaches the olfactory bulbs, next, the hypothalamus, next, the thalamus and midbrain, next the medulla, next the posterior horns of the spinal cord, next, the dorsal root ganglia and anterior horns The tracts most likely to conduct the advancing infection are olfactory nerves, the basal olfactory bundle (with an alternative route to Ammon's horn and thence through the fornix to the interbrain), the fibers connecting the hypothalamus with the thalamus and midbrain, the spinothalamic tract, spinal fibers to the dorsal root ganglia and anterior horns From the hypothalamus an alternative route of possible importance is through the neurones of the reticular formation to the

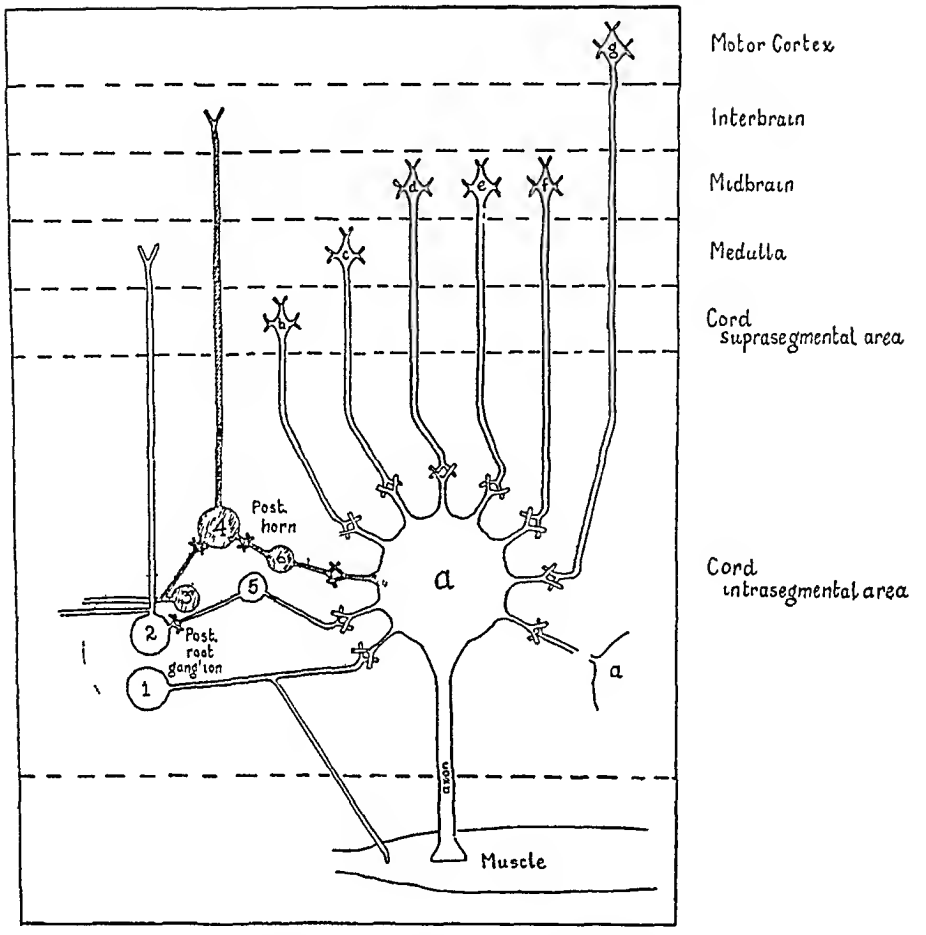

FIG 2 CHIEF CONNECTIONS OF THE ANTERIOR SPINAL HORN CELL

a, anterior horn cell, idiodynamic control *b*, intersegmental association cell, intersegmental reflex control *c*, cell of Deiter's nucleus, equilibratory control *d*, cell of red nucleus synergic control *e*, cell of superior colliculus, oculocephalogyric control *f*, cell of dorsal nucleus of Gudden olfactory control *g*, cell of precentral gyrus, voluntary inhibitory control (pyramidal tract) *1*, posterior root ganglion cell intrasegmental reflex control *2*, posterior root ganglion cell discriminative somesthetic impulses (columns of Goll and Burdach) *3*, Posterior root ganglion cell affective sensibility, pain and temperature (tract of Lissauer) *4*, Posterior horn cell, affective sensibility, pain and temperature (spinothalamic tract) *5* and *6*, intercalated, connector neurons

It will be noted that the only direct connection between the cord and the interbrain is through the spinothalamic tract, and that, while there are three direct connections between the midbrain and the anterior horn cells, only one of these (*f*, the "ancient olfactory motor pathway") is connected with the olfactory tract, and this is probably vestigial in man It would therefore appear that on anatomical grounds the chief connecting pathway between the olfactory tracts and the spinal cord is through the spinothalamic tract The presumptive pathway through which virus reaches the anterior horn cells and posterior root ganglia in poliomyelitis is shaded

midbrain, pons and medulla, and possibly to the anterior horn cells of the cord (lateral group), accounting particularly for bulbar and sympathetic disturbances

Blood supply

This subject has recently been reviewed by Cobb (105) For the present discussion it is only necessary to take up a few points bearing on the question of possible dissemination of poliomyelitis infection to the central nervous system through the blood stream For various reasons, some of which have already been mentioned, it is evident that the infection spreads through the nervous system along certain rather narrowly restricted pathways, affecting these more or less severely and sparing more or less completely adjoining and distant areas At times even within a given affected cell-area, some cells may be totally destroyed and their neighbors left apparently unaffected A consideration of the anatomy of the vascular supply of the brain and cord fails to reveal any explanation of the distribution of the lesions on the basis of the distribution or arrangement of the blood vessels In the brain the anastomoses of the smaller arteries and capillaries are so abundant as to ensure a perfectly even distribution of virus from the blood stream In the cord the distribution of the arteries is, to be sure, segmental in large part, though not without intersegmental anastomoses Modern descriptions are in agreement on the symmetrical arrangement of the arteries To explain the asymmetrical distribution of spinal lesions in poliomyelitis the early work of Kadyi (61) on the spinal arteries has been cited to the effect that the right and left branches of the central arteries supplying the anterior horns are given off at different levels, resulting in a difference of arterial supply to the right and left horns at a given level A reading of Kadyi's original article, however, reveals the fact that in the lumbar cord (where the lesions of poliomyelitis ordinarily are maximal) no asymmetry of the vessels was observed The explanation of the one-sided and otherwise non-uniform distribution of the lesions on the basis of irregular distribution of blood vessels has, moreover, the fatal defect that it would be valid only if gross embolism or thrombosis occurred It is, of course, clearly established that embolism and

thrombosis are not features of the pathology of poliomyelitis The peculiar and characteristic *perivascular* lesions of the disease remain to be considered

Perivascular channels

It is generally agreed that there is no true lymphatic system in the central nervous system As long ago as 1889, Kadyi noted (61) the absence in it of lymphatic trunks Dandy and Blackfan (17), Weed (102), and others have shown the slightness of the connections between the central nervous system and the extranervous lymphatic system, and the fact that eventual drainage of the cerebrospinal fluid is almost entirely into the blood stream

The perivascular spaces of Virchow-Robin, while not lymphatics in the strict sense, nevertheless appear to have the analogous function of conducting water and various contained nutritive and excreted substances from the blood to the tissues and from the tissues back eventually to the blood stream They can be followed along the smaller arteries and veins and capillaries, but do not unite to form large trunks In general their course appears to be relatively short and from the nervous parenchyma to the pial surface where they end either in the subpial spaces or debouch into the subarachnoid space itself Under suitable methods, they can be shown to constitute a system, probably closed, of continuous and communicating channels from the subarachnoid space to the perineuronal spaces surrounding the nerve cells and neuroglial elements (Mott (81), Weed (102))

Although the direction of flow in these channels has been much disputed in the past, the careful investigations of Weed make it clear that, as might be postulated *a priori*, it is normally from within outwards and that, as Weed concludes (101) "under conditions approaching the physiological, no passage of fluid from subarachnoid space to nerve-cell occurs" Only under special and severely unphysiological conditions does a reversal of flow occur, permitting regurgitation of fluid from the subarachnoid space toward the nerve tissue Such conditions are first, marked increase of pressure in the subarachnoid space, second, anemia of the nerve tissue (e g , after ligation of the arterial blood supply (81)), third, intravenous injection of strongly hypertonic solutions (102) All these, it will be observed,

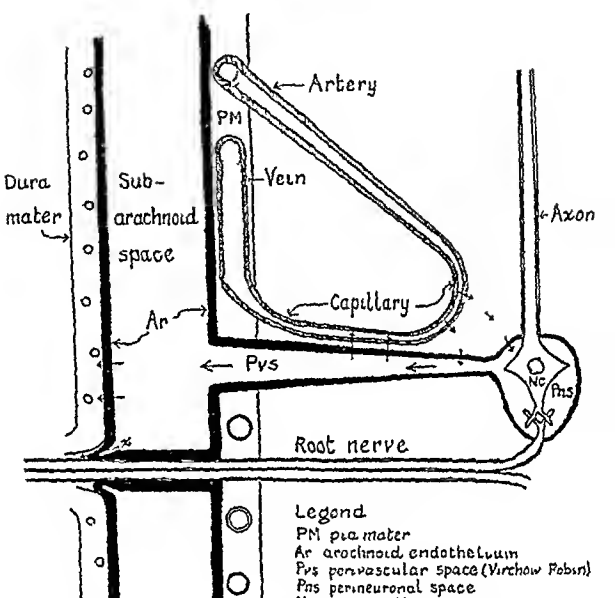

FIG 3 ANATOMICAL RELATIONS OF MENINGES, SUBARACHNOID SPACE, BLOOD SUPP OF THE NERVE TISSUE, PERIVASCULAR SPACE OF VIRCHOW ROBIN AND ITS PERINEURONAL EXTENSION, AND THE NERVE CELL

The perineuronal space is shown as part of a closed space, within an endothelial w in direct communication with the perivascular and the subarachnoid space, rather th discontinuous, as it is sometimes represented, with free openings into the tissue interstic Its exact limits in relation to the nerve fibers are unknown, and are arbitrarily shown the drawing at the ends of the myelin sheaths The outward direction of the current indicated by the arrows The relation of the perivascular system to the blood vessel also an approximation, and no endings such as probably occur in the spaces of the mater are shown The vessels in the pia mater are purposely indicated as being of grea than capillary diameter, since Kadyi states that no true capillaries are present in t layer It would appear that absorption of fluid from the central nervous system occ (*a*) within the nervous system proper from perivascular spaces into the intrinsic capillar (*b*) through the dural layer of the arachnoid into the capillaries of the dura, (*c*) throu the perineural arachnoid at the end point marked "r" in the diagram into the subdu spaces which are probably in communication with the extraneurous lymphatic syste The small arrows indicate the presumptive direction of fluid exchange from the arte segment of the capillary into the tissue, perineuronal and perivascular spaces, and b into the venous segment of the capillaries in the nervous tissue or dura, and into the subdu lymphatics

region of advanced cellular infiltration On the other hand, disintegrating cells can be seen in sections which are strikingly free from infiltration "

Hurst's (57) recent study of poliomyelitis in the monkey showed quite clearly the fact that, as he says "The nerve cells are primarily affected by the virus and their degeneration is not attributable to the accompanying interstitial inflammation "

The actual *priority* of the ganglion cell lesions to the interstitial lesions has been known for many years, though only recently has it received its proper emphasis in discussions of pathogenesis Thus, Leiner and von Wiesner (74) in 1910 experimentally demonstrated it by showing the presence of altered ganglion cells in the cords of infected monkeys on the third and fifth days after inoculation and before other changes or clinical symptoms had put in their appearance In the same year Landsteiner and Levaditi (70) reached the same conclusion, stating

> Quel est le méchanisme qui préside à la genése de ces lésions? Le fait que les cellules nerveuses offrent des altérations dégénératives à un moment où les infiltrations péri-vasculaires sont relativement peu prononcées, montre que le virus (ou les produits toxiques qu'il élabore) agit primitivement sur les cellules, et que la dégénérescence des neurones n'est pas sous la dépendance des lésions vasculaires

Finally the demonstration of intranuclear inclusions in nerve cells by Covell (16), Hurst (59), and Schultz (92) in monkeys infected with poliomyelitis completes the picture of this disease as a true virus infection of the nerve cells themselves

Since so much of the pathological studies in man—particularly the extremely exhaustive and painstaking studies of Harbitz and Scheel—has led pathologists to the conclusion that the vascular and other inflammatory ("interstitial") lesions come first and initiate the process leading to ganglion cell destruction, it should again be emphasized that save in exceptional instances, such as Rissler's third case, of overwhelming severity and fulminating course, the post mortem picture in man must necessarily present the features of primary lesion and secondary reaction so intimately and thoroughly intermingled as to make their disentanglement next to impossible The exception to

this rule which gives the clue to the true nature of the disease is that cited by Draper—normal cells in an abnormal milieu and, *vice versa*, abnormal cells in a normal milieu—and this is a point the significance of which has not been properly weighted until quite recently in most discussions of the pathology

Inflammatory lesions of the central nervous system

This term is preferable to the more commonly used "interstitial lesions" as being more comprehensive As here employed it includes all lesions other than degenerative changes of the ganglion cells themselves and includes the various changes secondary to the primary involvement of the nerve tissue proper For convenience, these may be considered in three main categories vascular, perivascular and meningeal lesions, changes in the supporting tissues themselves, changes in and about the nerve elements

In general the secondary changes in poliomyelitis are the same as inflammatory reactions in various other acute infections and consist of hyperemia, edema, cellular emigration, cellular proliferation, phagocytosis and removal of necrotic material

In poliomyelitis, dilatation of the capillaries and small veins is a striking feature of the picture, varying however, greatly in intensity in different areas The small vessels are indeed frequently so distended as to break with the greatest ease on post mortem manipulation, giving rise to the belief that hemorrhage is a part of the pathological process Hurst, however, believes that actual extravasation of blood does not occur during life to any marked degree

Even more striking than the hyperemia is the emigration of small cells into the perivascular spaces This, too, varies greatly in degree in different areas of the central nervous system but is—with the exception already noted—greatest in the most heavily infected areas, where wide collars of perivascular infiltration form a characteristic feature of the pathological histology In general, the infiltrations are most marked in the interior gray portions of the nerve substance, especially in the anterior horns of the cord They can be followed outward, especially along the veins (Wickman (104)) to the endings of the perivascular spaces under the pia (especially densely in the central fissure of the cord), and, discharging through the ostia into the sub-

arachnoid space, give rise to the pleocytosis and, doubtless, the increase in globulin, which is so characteristic and early a feature of the spinal fluid in the acute stages of the disease The arachnoid surfaces do not show, in poliomyelitis, deposits of inflammatory exudate such as are seen in ordinary forms of meningitis, and in relation to the so-called "meningeal" signs and symptoms that will presently be discussed this point should be kept in mind

The cells in these perivascular infiltrations are mainly lymphocytes with some polymorphonuclear leucocytes (Hurst (57)) the aggregate mass of such cells in a case of poliomyelitis of any severity must be enormous

In the tissues outside the perivascular spaces, edema and increase of cells is found with varying intensity and probably a little later than the perivascular infiltration The cells are partly polymorphonuclear leucocytes which have doubtless passed through the capillary and pericapillary cell membranes by virtue of their powers of locomotion, and, as Hurst (57) has so clearly shown, consist mainly of fixed cells that have undergone metamorphosis and probably proliferation, the microglial cells. These are identical with the "polyblasts" of Wickman who erroneously ascribed their origin to lymphocytes A few true lymphocytes may occasionally be found

After death, the ganglion cells are invaded and removed by both the polymorphonuclear and the microglial cells The process of neuronophagia is particularly prominent in the later phases of the acute stage of the disease and may be detectible for a considerable period thereafter

Summary For the sake of emphasis in relation to the general purpose of the present discussion of the subject, some of the features of the disease process may be re-capitulated *The first attack of the disease is upon the nerve cells* which are injured in varying degrees *Secondary to this attack is a reaction, essentially defensive and reparative,* including vascular dilation, emigration of lymphocytes and leucocytes into the perivascular spaces, often to the point of dilating and apparently obstructing them, interstitial edema, emigration of leucocytes, metamorphosis and proliferation of the microglial cells, neuronophagia The perivascular infiltration follows the spaces of Virchow-Robin in the normal direction of flow of these channels to the spaces

under the pial sheaths of the central nervous system and into the subarachnoid space There is no true meningitis

Distribution of the nervous lesions

It is unfortunate that the attention of the pathologist has frequently been concentrated on the lesions of the cord to the exclusion of those elsewhere in the central nervous system Wickman (104), Harbitz and Scheel (50), Muller (82), and a few others have, however, given us detailed descriptions of the pathology of the central nervous system as a whole, and it is on these that we base the present review, noting that we must depend mainly on the inflammatory lesions for our evidence rather than on ganglion cell changes which have been less systematically reported

Within the cranial cavity, the nervous structures show marked and roughly constant differences in degree of reaction In a general way, vascular dilatation and the infiltrations in and around the vessels are slight in the cerebral cortex and cerebellum, much more marked in the brain stem

Olfactory bulb

Little or no attention appears to have been devoted to the pathology of the olfactory bulb in poliomyelitis It is a familiar fact that, unless special care is observed, the olfactory bulb, firmly attached as it is by the numerous olfactory nerves, is likely to be torn off when the brain is removed at necropsy, and so fail to be examined This is the only explanation that occurs to me for the uniform failure to note either the macroscopic or the microscopic appearance of the structure in the protocols available in the literature Harbitz and Scheel briefly note in one case that the olfactory bulb was normal—the only instance in which I have found it mentioned The subject is certainly one deserving further study, especially since in the similar Borna disease of horses the olfactory bulb is the seat of constant and characteristic changes

Cortex

As a rule, the neopallial portions of the cortex show nothing more than slight and scattered areas of vascular dilatation and occasional

slight infiltrations of small cells The central gyri are sometimes the seat (Wickman, Harbitz and Scheel) of somewhat more marked changes, not, however, severe On the other hand, the areas bordering on the Sylvian fossa, particularly the inferior temporal gyri, are as a rule more severely affected These gyri belong to the archipallium, and comprise the hippocampal and uncinate gyri, which together with the gyrus fornicatus, constitute the cortical associative areas of the sense of smell and are, as will be shown, directly connected with the olfactory lobes These gyri were almost uniformly affected in the cases of Harbitz and Scheel Muller also noted a heavy involvement of one or more of them in two of his cases Hurst has recently made the highly significant observation that in his monkeys Ammon's horn was involved in animals infected by the olfactory route, not in those inoculated by intracerebral injection

Brain stem

In the brain stem, the lesions show certain areas of predilection Harbitz and Scheel repeatedly note and comment on the frequency and relative severity of involvements in and near the Sylvian fossa, at the anterior part of the basis cerebri, and in the basal ganglia This area includes the anterior perforated space, the areas surrounding the optic chiasms, the infundibulum, tuber cinereum, corpora mammillaria, the feet of the cerebral peduncles, the interpeduncular space Of the basal ganglia the optic thalami suffer most frequently and severely It will be noted that the interbrain, especially the hypothalamus and thalamus, is therefore the site of quite constant lesions of moderate or greater severity In rare cases the lesions are almost limited to this area The main details of such a case, reported by Harbitz and Scheel (50), are as follows A child of 7 years became suddenly ill with fever, somnolence, and twitchings in the left arm and leg, dying on the fourth day An acute encephalitis of the left optic thalamus was found, with edema, hemorrhage, softening and intense cellular infiltration Lesions were not found in other parts of the central nervous system Thirteen cases of poliomyelitis occurred in the same city (Kristiania) suggesting that this case was of the same nature

In the midbrain, lesions are also frequent and sometimes severe

Thus, Harbitz and Scheel noted with especial frequency typical changes in or near the red nucleus and the substantia nigra A peculiarity of distribution is that in the midbrain, the lesions are as a rule at or below the level of the aqueduct (tegmental region) and rare in the tectal portion (corpora quadrigemina, etc) which is mainly concerned with visual function The oculomotor nuclei are occasionally but exceptionally involved

The gray matter of the pons and medulla shows more severe and even more constant changes, but with local differences To quote Harbitz and Scheel

In the actual white substance, the signs of inflammation were relatively slight, almost free of inflammation (apart from a marked hyperemia) were the pyramids, the most anterior parts of the pons, the olives likewise *but little was found in the nuclei of the columns of Goll and Burdach* and in the crura cerebelli Strongly marked on the other hand was the inflammation in the gray substance and specifically, in the posterior and medial parts of the medulla oblongata and pons, *above all, in the substantia reticularis with its numerous groups of ganglion cells*, also in the entire floor of the fourth ventricle were seen inflamed and infiltrated vessels, but the inflammation as a rule was more marked in the form of numerous larger and diffuse foci in the deeper layers of the substantia reticularis

As regards the cerebellum, Harbitz and Scheel found little except a meningeal reaction especially in the portions adjacent to the medulla and pons They say "In the substance of the cerebellum the signs of inflammation were slight throughout, especially in both hemispheres where it was almost absent" In some cases some changes were found in the dentate nucleus, inferior vermis on the whole, in parts bordering on the medulla and passing over into the latter"

In the spinal cord itself, the distribution of changes is so well known as perhaps not to require exhaustive review The cervical and lumbar enlargements are the seat, as a rule, of the most severe and extensive changes The posterior horns are perhaps almost as frequently, but by no means as severely, affected as the anterior, where the cell degenerations reach their height The columns of Clarke are frequently, occasionally severely, involved No particular localization within the anterior horns is constant, all groups including the lateral, being noted in one case or another as involved

The frequency of involvement of the intervertebral ganglia in man was first noted by Forssner and Sjovall (48), and by Cadwalader (11), who found lesions in them in practically all cases, as a rule associated with lesions in the posterior horns of the cord With the exception of Harbitz and Scheel, all investigators who have paid attention to these structures have found them involved Even Harbitz and Scheel, who concluded that they did not show definite signs of inflammation, noted in some of their cases an infiltration with polymorphonuclear leucocytes The demonstration by Flexner and Lewis (42), Flexner and Clark (36), and Flexner, Clark and Amoss (39), of virus in these structures during the early, preparalytic period of the experimental disease is highly significant, and it is noteworthy that the virus was also found (39) in an intervertebral ganglion of a human case

Changes in the peripheral nerves have not been found during the acute stage of the disease

As respects the white substance—besides some perivascular infiltrations which probably originate in the gray matter—early degenerative changes in the nerve fibers have occasionally been detected Thus, Rissler (90) found swellings and peculiar tortuosities and beadings of axis cylinders Such changes are doubtless indications of death of the nerve cells

Summary We may briefly summarize the distribution of the lesions in the central nervous system as follows

1 Relative freedom of the neopallial cortex

2 Frequent, moderate involvement of the archipallial (olfactory) cortex

3 Frequent, moderate to severe involvement of the interbrain, especially the hypothalamus and thalamus

4 Frequent, moderate involvement of the tegmental portions of the midbrain

5 Relative freedom of the cerebellum

6 Frequent, moderately severe, involvement of the gray matter of the pons and medulla, especially the region of the floor of the IV ventricle, formatio reticularis and bulbar nuclei, excepting the cuneate and gracile

7 Moderate or moderately severe involvement, in the cord, of the posterior horns and intervertebral ganglia, the latter, at least, being involved before paralytic signs appear

8 Maximal involvement, in so far as ganglion cell degeneration is concerned, of the anterior horn cells

Lesions in tissues outside the central nervous system

Some space finally must be devoted to a discussion of the pathological changes found with considerable frequency, though without absolute regularity, in tissues outside the nervous system Harbitz and Scheel (50) state (p 108) that the findings were in most cases negative

Frank signs of a general infection such as we assume to be present from the first beginnings of the disease were usually not found, to be sure, as has been mentioned, most fatal cases do not occur till the seventh to ninth day after the onset of the disease, swollen spleen was, however, demonstrated in case X In the intestinal canal, also, normal conditions were found The view expressed by one of us (Harbitz), that acute poliomyelitis in some cases might have found the intestinal canal as a possible atrium, therefore finds no support herein

It is interesting in view of the frequently preceding angina, to which significance has also been attributed as an atrium, to note the result of our investigations of the neck and nose In case VIII, the tonsils and throat were pale and without signs of inflammation, in case XI the throat and nose were very closely examined (also microscopically) with negative results, in case XIII, nothing abnormal was found also in the accessory sinuses of the nose

Wickman (104) apparently found extranervous lesions somewhat more frequently He says

Since the Heine-Medin disease is an infectious disease, one can expect signs of a general infection to be demonstrable In fact, too, swelling of the spleen is present in many cases, at times cloudy swelling, indeed even a manifest inflammation of the kidneys appears Exceptionally, subpericardial and subpleural hemorrhages are observed which are perhaps, at least in part, to be attributed to the respiratory disturbances setting in toward the end More frequently than the changes mentioned there appear a swelling of the lymphoid apparatus of the intestine, the Peyer's patches and solitary follicles, as first mentioned by Rissler Whether this is to be ascribed to a local action of the poison or to the general infection is at present uncertain Benecke found a moderate swelling of the tonsils with purulent deposits

More important, and these changes are *alone characteristic of the disease, however, are the changes in the central nervous* system (Italics added)

Muller (82) says (p 32)

Gross and constant lesions, characteristic of poliomyelitis, in the internal organs were not found in our autopsies In our sectioned cases in which an enteritis was usually clinically absent, the anatomical changes in the intestine in the form of swelling of the solitary follicles and the mesenteric lymph-nodes, as well as reddening of the mucosa, were relatively slight and inconstant Also, tumors of the spleen are by no means regularly present, in acute poliomyelitis generally they customarily attain only moderate size The heart was shown macroscopically to be healthy The hyperemic liver and the kidneys often show parenchymatous degeneration, in the adrenals, pancreas, thyroid, parotid and thymus substantial findings were absent in our cases

Considering the character of the above plain statements, which include (Harbitz and Scheel, and Wickman) an assumption that poliomyelitis is a general infection, and also an estimate of the frequency and character of the extranervous lesions, the writers of the Rockefeller Monograph (86) are not quite accurate when they say (pp 19 et seq)

The attention of observers has been almost wholly centered on the lesions of the central nervous system, and in consideration of the fact that the most striking disturbances, both pathological and clinical, are associated with the nervous system, this is not remarkable In view, however, of the very definite and constant changes which are found at autopsy in other viscera, it is rather strange that they should have been almost wholly disregarded, and that so little emphasis should have been put on the fact that acute poliomyelitis is essentially a general infection Rissler, Harbitz and Scheel, and Wickman have all noted the presence of lesions outside the nervous system, but have passed them by as having little bearing on the disease As a matter of fact, the recognition of acute poliomyelitis as a general infection has an important bearing both in explaining the clinical course of the disease and as affecting any possible means of treating it

They go on to say (pp 22 et seq)

The changes which are found in other organs in acute poliomyelitis are less striking than those in the nervous system, but they have been, in our

experience, practically as constant In all of the eleven acute cases which we have been able to examine, there has been more or less extensive involvement of the lymphoid tissue and of parenchymatous organs The lymphoid tissue throughout the body appears to react to the virus The Peyer's patches of the intestine and the mesenteric glands show perhaps the most marked acute swelling The mucosa over the Peyer's patches is, however, unaffected There is also definite, and sometimes pronounced enlargement of the substernal, bronchial, cervical, axillary, and inguinal lymph glands and of the tonsils The spleen is frequently somewhat enlarged, and on section the Malpighian corpuscles stand up in raised, pale, obviously translucent nodules The thymus shows changes identical with those in the lymphoid tissue elsewhere *The reaction is, in general, the same throughout the lymphoid tissue, regardless of its location* On histological examination some of the lymphoid nodules may present a normal appearance, but the majority consist of a zone of lymphocytes surrounding a more or less sharply circumscribed pale center High magnification shows the center of the lobule to consist chiefly of large endothelial cells with oval vesicular nuclei These cells are similar to the cells lining the lymph sinuses, but most of them are larger, more swollen, and take the stain very lightly Sometimes the nuclei look like pale shadows, and the outline of the protoplasm is so faint that it can scarcely be distinguished The better preserved of these cells are markedly phagocytic and frequently contain many particles of necrotic cells These cell inclusions are surrounded by a lightly stained halo and are apparently situated in vacuoles in the protoplasm Scattered throughout the center of the nodule are many broken down cells and granular fragments of necrotic nuclei The cells which are going to pieces are for the most part lymphocytes, but the endothelial cells also seem to swell up and finally disintegrate In areas with extensive necrosis there is often an invasion by polymorphonuclear leucocytes

In the lymph sinuses there are also large numbers of the same phagocytic endothelial cells Many of them are of great size and contain necrotic fragments of nuclei, whole lymphocytes, or numbers of red blood corpuscles In the lymph sinuses, there is extensive proliferation of the endothelial cells, as is evidenced by the frequency with which mitotic figures are found Numbers of necrotic cells are met with in the lymph sinuses, but, in general, necrosis is a more prominent feature in the centers of the lymphatic nodules, and proliferation in the lymph sinuses

Among the parenchymatous organs, "cloudy swelling, such as has been frequently described, is usually met with" The focal necroses

in their order of frequency at various stages of the acute period Those plainly or presumptively of nervous origin have been starred (*) The reasons for regarding some of the symptoms (e g , vomiting) as nervous will be given in the subsequent discussion

Table 2 gives a list from another epidemic, with a still larger number of cases

TABLE 1

New York Epidemic of 1907, about 746 cases, La Fetra and Schwarz (67), symptoms of the first few days

Fever	684
Pain and tenderness	472*
Restlessness	369*
Apathy	294*
Vomiting	276*
Constipation	220
Headache	162*
Diarrhea	143
Rigidity of the neck	121*
Stupor	71*
Delirium	62*
Chills	61
Convulsions	51*
Rapid heart	37
Photophobia	26*
Rapid respiration	20
Dysphagia	19*
Sore throat	18
Respiratory abnormalities (irregularities?)	14
Cardiac abnormalities (slow, irregular)	8*
Twitchings	8*
Sluggish or irregular pupils	6*
Retention of urine	5*
Numbness	3*

Allowing for some differences in terminology, the early symptoms in these two large series may be combined to give a somewhat clearer picture of the preparalytic stage as a whole The 10 commonest symptoms, or symptom groups, are given in table 3

Muller's (82) series of 58 cases—from which the preparalytic symptoms have been tabulated as a whole—deserves separate consideration Muller apparently followed a systematic plan of questioning in ob-

taining his histories which resulted in a much fuller description of the early symptoms and brought out certain highly significant data not

TABLE 2

New York Epidemic of 1916, 1500 cases, New York Board of Health Report (80), symptoms at the time of onset

Fever	806
Nausea and vomiting	476*
Malaise and weakness†	255
Headache	205*
Constipation	148
Irritability	125*
Diarrhea	122
Coryza	78
Rigidity of neck	74*
Tonsillitis	65
Peripheral pain	57*
Twitchings	57*
Pharyngitis	57
Prostration†	49
Convulsions	47*
Cough	45

† Malaise, weakness and prostration probably are insufficiently descriptive terms for what were probably in many instances definitely nervous disturbances The common initial drowsiness of poliomyelitis, not mentioned in the list, may be included under prostration

TABLE 3

Ten commonest early symptoms, tables 1 and 2

Fever	1,490
Nausea and vomiting	752*
Pain and tenderness	529*
Irritability, restlessness	494*
Apathy, stupor, prostration	414*
Constipation	368
Headache	367*
Diarrhea	265
Rigidity of neck	195*
Coryza	78

noted in earlier reports The summary (table 4) is mine, made from the case reports in his monograph

A rough grouping of the symptoms noted in Muller's series may be attempted and is of some interest (table 5)

Muller's case reports and his discussions bring out rather forcibly the facts first, that the restlessness of this stage of poliomyelitis is usually a nocturnal phenomenon, frequently associated with drowsiness by day (a genuine sleep reversal, in fact, apparently quite like that of lethargic encephalitis), that disturbances of the vegetative nervous system and mechanisms are very frequent, that psychic dis-

TABLE 4

Fifty-eight cases, Hesse-Nassau Epidemic of 1909 (Müller), preparalytic symptoms in order of frequency

	NUMBER	PER CENT OF CASES
Fever	48	83
Sweating	30*	52
Restlessness	30*	52
Hyperesthesia, general	26*	45
Lassitude	26	45
Loss of appetite	25	43
Drowsiness	22*	38
Constipation	22	38
Vomiting (21), nausea (1)	22*	38
Pains, localized	18*	31
Headache	11*	19
Diarrhea	10	17
Urinary disturbances	9*	16
Cough	9	16
Stiff neck	8*	14
Snuffles	5	9
Stiff spine	5*	9
Rolling of eyes	5*	9
Chills	5	9
Twitchings	4*	7
Other symptoms (each less than 4 times)	36	
Total symptoms	376	

turbances—a point to which we shall return—are also common, that frank sensory disturbances (usually generalized at the very onset) are also common, that primary respiratory disturbances are relatively uncommon, that, of the gastrointestinal disturbances, few point to an actual gastroenteritis (this point will also be again discussed), and that "meningeal" disturbances are not infrequent, altogether, a cerebrospinal, rather than a "systemic," complex of symptoms

TABLE 5

Classification of symptoms in Muller's cases

	NUMBER		PER CENT OF TOTAL SYMPTOMS
A Fever (48) and chills (5)		53	14 1
B Disturbances of sleep		55	14 6
Drowsiness, alone	9		
Drowsiness by day (with restlessness at night) (sleep reversal)	13		
Restlessness, alone	9		
Restlessness at night	8		
Restlessness at night (with drowsiness by day)	13		
Sleeplessness	2		
Bad dreams	1		
C Subjective and miscellaneous psychic or cerebral disturbances		42	11 2
Lassitude (usually extreme)	26		
Rolling of eyes	5		
Gnashing of teeth	2		
Peevish, irritable	2		
Convulsions	1		
Delirium	1		
Apprehensiveness, apathy, weeping, feeling of weakness, staring look, each 1	5		
D Disturbances of vomiting mechanism		47	12 5
Vomiting	21		
Nausea	1		
Loss of appetite*	25		
E Sensory disturbances		50	13 3
Hyperesthesia, general	26		
Hyperesthesia, localized	5		
Pains, localized	18		
Paresthesia	1		
F Meningeal and/or posterior horn, root or ganglion disturbances		25	6 7
Headache	11		
Stiff neck	8		
Stiff spine	5		
Stiff legs (with pain)	1		
G Disturbances of vegetative system		64	17 0
Sweating	30		
Constipation	22		
Bladder dysfunction	9		
Salivation	1		
Tachycardia	1		
Pallor	1		

* Vide Dumpert (21)

TABLE 5—*Concluded*

	NUMBER		PER CENT OF TOTAL SYMPTOMS
H Miscellaneous nervous disturbances		9	2 4
Twitchings	4		
Weakness (local)	2		
Unsteady gait	1		
Vertigo	1		
Tinnitus	1		
I Respiratory tract disturbances		21	5 6
Cough (slight, 6)	9		
Snuffles	5		
Bronchitis	3		
"Angina" (2), tonsillitis (1)	3		
Hoarseness	1		
J Primary digestive disturbances		10	2 7
Diarrhea	10		
Total symptoms of nervous order (groups B, C, D, E, F, G, H)		292	77 6
Fever, chills, (group A)		50	14 1
Other symptoms (groups I, J)		31	8 3

The three series of cases, as has been said, throw together all the symptoms of the preparalytic phase of the disease If we are interested in separating those of the very beginnings of the disease from the subsequent, but still preparalytic, symptoms we may turn to the 34 case reports of the Rockefeller Monograph (86) and the 81 of Draper's "Acute Poliomyelitis" (19), where an effort has been made to record the symptoms in the chronological order of their development

For convenience, in the ensuing pages the symptoms will be divided into four groups representing four successive phases of the disease, defined as follows

First phase symptoms at the very beginning,

Second phase. symptoms subsequent to the onset but preceding the appearance of paralysis,

Third phase· symptoms present at the onset of paralysis,

Fourth phase period of recovery

While the dividing line between the different phases is in some degree artificial and, as will be seen, a considerable amount of overlapping occurs, the grouping will be found to correspond with actual

TABLE 6

One hundred fifteen cases, initial symptoms, first phase, Rockefeller Monograph and Draper

	NUMBER	PER CENT OF CASES
Fever	75	66
Vomiting	35	30*
Drowsiness	30	26*
Restlessness, irritability	29	25*
Headache	25	22*
Vague†	22	20
Pain or hyperesthesia	21	18*
Constipation	14	12
Loss of appetite	10	9
Apathy, quiet, listless	10	9*
Diarrhea‡	7	6
Chills	4	3
Sore throat	3	3
Stiff neck	3	3*
Sweating	2	2*
Tonsillitis	2	2
Slight cough	2	2
Twitching	1	1*
Vertigo	1	1*
Initial paralysis	1	1*
Total symptoms	297	

† "Felt poorly," "felt sick," "indisposed," "taken sick," "appeared ill," "not quite so well as usual," "ill," "gone feeling in stomach," "tired feeling," "seemed dull"

‡ Noted as "slight" in 5 cases, as "green stools," in 1, as "a colitis" (apparently of 1 day duration), in 1, no further description or note, in 1

TABLE 7

Summary

	NUMBER	PER CENT OF TOTAL
Total symptoms of nervous order	158	53 2
Fever	75	25 2
All other symptoms	64	21 6
Or, for comparison with the next table, if we exclude fever		
Nervous symptoms	158	71 1
Other	64	28 9

qualitative differences in symptoms and in some instances to be marked by definite intervals of symptomatic silence between phases

Tables 6 and 7 have been made by myself from the 115 case reports in the two monographs

It will be noted that among the "other symptoms" are included constipation, loss of appetite and the "vague" group The sig-

TABLE 8

Later preparalytic symptoms, second phase, Rockefeller Monograph and Draper

	NUMBER	PER CENT OF CASES
Fever (not always specifically mentioned, probably always present)		
Pains, tenderness, hyperesthesia	*37*†	*32**
Stiff neck	*36*	31*
Neck or spine painful on flexion	*28*	24*
Headache	28	24*
Drowsiness, stupor	26	23*
Vomiting	25	22*
Restlessness, irritability	20	17*
Constipation	18	16
Apathy, quiet, listless, dull	12	10*
Twitching	12	10*
Loss of appetite	7	6
Ataxia	6	5*
Retention of urine	5	4*
Delirium, irrational, clouded consciousness	4	3*
Apprehensiveness	3	3*
Local weakness, without paralysis	3	3*
Tremor	3	3*
Convulsions	2	2*
Sweating	2	2*
Wild behavior, nystagmus, choreiform movements, clonus, diarrhea, cough, each 1 (4*)	6	*
Total symptoms	283	

† Symptoms in italic show great increase in frequency in second phase as compared with first phase

TABLE 9

Summary

	NUMBER	PER CENT OF CASES
Nervous symptoms	256	90 5
Other (constipation, 18, loss of appetite 7)	27	9 5

nificance of these and other symptoms will be presently discussed The very small number of frank respiratory and primary gastrointestinal disturbances should be noted

The subsequent, preparalytic symptoms (second phase) in the same series of cases are listed, also in order of frequency, in table 8

In Draper's 81 cases, the knee jerks at the first examination (nearly all in the preparalytic stages) were increased on one or both sides 31 times, doubtful, 7 times, absent, 8 times, normal, 7 times, unequal, 7 times, the Kernig sign was positive 16 times, doubtful once Notes on these signs are not given in all cases

Forty of the 115 cases did not develop paralysis The symptoms present at or very shortly after the onset of paralysis (third phase) in the remaining 65 cases are shown in the following table

A comparison of the symptomatic differences at the successive periods in the acute stage of poliomyelitis is afforded by the relative frequencies of the different symptoms in the last three tables Thus, the five commonest symptoms other than fever in order each are

First phase Vomiting, drowsiness, restlessness/irritability, headache, vague (mostly subjective),

Second phase Pains/tenderness/hyperesthesia, stiff neck, pain on flexion of neck or spine, headache, vomiting,

Third phase Paralysis, pain on flexion of neck or spine, drowsiness, pains/tenderness/hyperesthesia, vomiting

Without forcing the statistical analysis of a relatively small number of cases with histories necessarily somewhat incomplete, it is fair to conclude, first, that the predominant symptoms in all phases are of a nervous order,[8] second, that they suggest a certain order of progression that may well be compatible with a characteristic mode of advance in pathology within the central nervous system This order of advance in a general way would appear to be, cerebral (intracranial)—lower sensory—lower motor

In attempting to define somewhat more closely, on the basis of the clinical manifestations, the probable origin of the symptoms and, from the origin, the route followed by the advancing infection, it is necessary to discuss some of the symptoms in detail

First phase

While the first phase is seen from the tabulation of symptoms to consist of a complex of fever, drowsiness/apathy/listlessness, alter

[8] Amoss (2) has recently remarked of the onset symptoms "Any of the symptoms mentioned may result from involvement of the central nervous system"

nating with restlessness and irritability, headache, vomiting, loss of appetite, hyperesthesia, pains, constipation or diarrhea, and other less frequent symptoms, certain parts of the picture do not come into clear focus until more detailed clinical descriptions are supplied At this period of the disease there is a *psychic change* closely associated with *disturbances of sleep* which in some degree or other is very frequent and characteristic With it in a certain, undetermined proportion of cases, is associated a *general hyperesthesia* that Muller differentiates from the local tenderness and pain so frequent at a somewhat later stage, and which appears to consist of a heightened sensitiveness to stimuli, especially painful, from all parts of the body Draper (19) gives a beautiful description of the peculiar *psychic changes* at the onset Considerably condensed it is as follows

there seems to be little doubt in the minds of those who have seen much of the earliest hours of the disease that a very definite and characteristic clinical picture presents itself But it is difficult by descriptive method to transfer an adequate impression of the subtile and striking difference between the onset hours of infantile paralysis and those of any other of the acute infectious diseases of childhood To say that the temperature is elevated, often as high as 103° or 104° and that the child is flushed and miserable, that vomiting often occurs and that drowsiness supervenes, does not offer sufficiently distinguishing evidence of the special type of infection Nevertheless, this common symptom complex is shot through with delicate manifestations that are unmistakably specific, but which must still be viewed as clinical impressions—those helpful though indefinite aids in diagnosis

Now when infantile paralysis becomes epidemic in a locality which has been previously free from its presence, the physicians in that territory soon appreciate this difference from the usual illnesses of children there is a look of mingled apprehension and resentfulness, quite unlike the alert, bright and shining eye of other fevers. The psychic change responsible for this look finds further expression in a characteristically annoyed shrugging of the shoulder which occurs when the child is touched or simply spoken to Indeed there is frequently a snarling whine of resentment which is synchronous with this gesture of discontent (In) cases of overwhelming infection there are other striking phenomena The child is restless, breathes rapidly and seems to be busily and actively resisting some incomprehensible disturbance of its usual comfort In these in-

stances, the irritability and resentful manner are not marked, but the whole organism seems to be composed of tensely drawn wires—a universal overstimulation This pressor state of the nervous system is so marked that a sort of impulsive ataxic tremor is present in every motion, especially when that motion has intent It is interesting to recall at this point that the very earliest symptoms in the monkey are not at all unlike those just described, for the animal becomes highly excitable and seems to develop the same state of intense excitability of the entire nervous system Usually a few cases are met with whose profound stupor masks all other signs and symptoms

Muller's description brings out the associated *disturbances of sleep*, and some other points He says

Only at the beginning of the disease have we seen marked psychic disturbances Only exceptionally have there been clouding of consciousness and delirium Even in fatal cases the sensorium usually remained clear till death But quite frequently during the first days of illness the children were strikingly sleepy The little ones often slept night and day "sie wurden von selbst fast gar nicht wach" This sleepiness during the daytime, which was to be looked on as a certain apathy and light somnolence, was accompanied by a marked restlessness during the night This restless sleep was accompanied by frequent crying-out, confused dreams, raving, starting, tossing about and pushing up to the head of the bed This restless sleep, disturbed by paroxysmal crying has already been observed by Heine He also emphasized the fearfulness of the little patients In fact, the children whose expression was not uncommonly described as fixed (starr), were often restless, tearful, peevish, irritable and anxious For the greater part this was the result of the "hyperesthesia" In a two year old child the initial sleepiness was interrupted by a one day period of pathological vivacity, with a great and precipitate loquaciousness

These experiences harmonize with those of other observers They describe as especially outstanding the restless, tearful, anxious and irritable state of the children

At this point we may also note Muller's description of certain other symptoms common at the very onset of the disease Muller is almost alone in calling attention to the finer details of some of the neurological findings Of *hyperesthesia*, he says

We have described the extraordinary painful sensitiveness of the children to every touch and passive motion at the beginning of the disease as an

extremely frequent and correspondingly pathognomonic early symptom This hyperesthesia is very easily overlooked, since it usually appears early and soon afterwards disappears In almost nine-tenths of all our cases this hyperesthesia was present Its clinical picture varied As a rule we were apparently dealing with a skin hyperesthesia beginning very early Even with the most cautious examination by the doctor—indeed, when the mothers gently laid hands on the children—they would begin to cry loudly In their anxiety not to be touched they not infrequently, even at the approach of members of the family, drew the bedclothes over their heads At any attempt to care for them, the children held fast to the bedclothes and often cried if these were taken away This hyperesthesia to touch affected almost the entire body Many children during the early beginnings of the disease, despite their frequent psychic unrest, tearfulness and anxiety, lay as quietly and still in bed as possible

Sweating was also frequently noted by Muller, less frequently by other observers Muller says

> The second important cardinal symptom of the early stage is the striking tendency to sweating We found it in three-fourths of our cases Usually the severe outbreaks of perspiration occur only during the first days of the illness or only at the very onset the whole body seems to participate in it Often the tendency to severe sweating is marked for weeks or even months [9]

Gastrointestinal and genitourinary disturbances constitute another important group of early symptoms of these *vomiting* is the most common, *constipation* less so, and *diarrhea* least The incidence of diarrhea varies greatly in different epidemics, but a certain number of cases is observed in practically all Loss of appetite is even commoner than constipation and only less common than vomiting Early *retention of urine* was comon in Muller's series and occasionally noted in others The origin of these and other symptoms is to be presently discussed and the associations of gastrointestinal and other symptoms, especially, is therefore of considerable interest From a tally of

[9] The epidemic from which Muller's cases were drawn apparently ran from August, 1909, to January or February, 1910 Its height was attained in October and November during which two months 40 of his 58 cases had their onset The frequent sweating therefore was probably not related to hot weather

Draper's 81 cases vomiting was associated with fever 14 times, with headache and drowsiness each, 6 times, with pains or hyperesthesia, 3 times, with restlessness/irritability, 3 times, and with other symptoms not more than once each Constipation (10 cases) was associated with restlessness/irritability 5 times, with vomiting, 3 times, with headache and drowsiness each twice, with the vague group of symptoms, twice, and with no other more than once Diarrhea (5 cases) was associated with drowsiness twice, vomiting once, and with no other symptom more than once The diarrhea did not in these cases appear to have the character of a true enteritis Not only was it slight but it was in all cases quite transient, and marked by absence (in the record, at least) of pain, tenesmus, bloody stools, dehydration, etc In some of the epidemics, there has undoubtedly (as Muller remarks) been a coincident epidemic of enteritis, since both diseases are characteristically of the sumer months and the same age group of young children and infants This was not the case in some other epidemics, such as that of 1916 on which Draper's study was based, and here it would seem fair to describe the diarrhea as nothing more than a transient increase of peristalsis without enteritis It is perhaps significant that diarrhea has been noted in the early stages of experimental poliomyelitis in the monkey by various investigators, even after intracerebral inoculation (Flexner and Lewis (46), Romer (91))

The *constipation*, as well as the bladder disturbances, in poliomyelitis have certain features that deserve attention They both appear to be due to some interference with the relaxing mechanism of evacuation rather than to paresis of the musculature Meteorism is rarely seen in connection with the constipation, and Muller noted that attempts at micturition were usually accompanied by pain (spasm?) Both these appear to be of nervous order, with interference in autonomic control Muller classes them together as due to paresis of the musculature

The *vomiting* of poliomyelitis is not characteristically projectile (Rockefeller Monograph), not often associated with headache (once only at the onset in Draper's), but has no relation as a rule to the ingestion of food or indiscretions of diet nor to other gastrointestinal disturbances (in Draper's cases, once associated with diarrhea and three times with constipation in the 14 cases) It seems highly prob-

able that the vomiting of poliomyelitis is usually, if not always, of central origin

The *headache* so frequently present at the onset also has certain peculiarities It may be frontal or occipital or general It is rarely if ever hemicranial It is frequently associated with vomiting (6 times in Draper's cases) It is sometimes associated with stiff neck, but not as a rule

TABLE 10

Signs and symptoms at or soon after onset of paralysis (65 cases), third phase, Rockefeller Monograph and Draper

	NUMBER	PER CENT OF CASES
Fever (almost always present—not always specifically stated)		
Paralysis	65	100*
Neck or spine painful on flexion	27	42*
Drowsiness (22) and coma (1)	23	35*
Pains, tenderness, hyperesthesia	22	34*
Vomiting	10	15*
Restlessness and irritability	8	12*
Constipation	9	14
Red throat	7	11
Headache	4	6*

Other symptoms noted less than 3 times each

Summary

	NUMBER	PER CENT OF CASES
Nervous symptoms	150	85 8
Other	25	14 2

Less frequent or less frequently noted symptoms of the early stage are tachycardia, cardiac arrhythmias, flushing of the face, rapid respiration, dilatation of the pupils, photophobia (Muller)—all suggestive of vegetative dysfunction

Summary The symptoms of the initial stage may reasonably be grouped somewhat as follows

(a) Psychic, "affective," disturbances without loss or clouding of consciousness, apprehensiveness, anxiety, fear, awareness of present or

impending bodily disturbance, all of which may be summed up as a disturbance of "feeling tone"

(b) Disturbances of the mechanism of sleep, drowsiness, restless sleep, insomnia, sleep reversal minor degrees seen in apathy, listlessness,

(c) Disturbances of the vegetative system, sweating, flushing, disturbed intestinal peristalsis, disturbed autonomic control of rectum and bladder, tachycardia, dilatation of the pupils

(d) Disturbances of the mechanism of vomiting, vomiting, nausea, loss of appetite

(e) Disturbances of the general sense reception, particularly of pain, general hyperesthesia, heightened reactivity to sensory stimuli,

(f) Headache,

(g) Disturbance of temperature regulation, fever

Sources of the nervous symptoms

(a) The source of the *psychic or affective group of symptoms* is suggested, by their character and by the absence of loss or clouding of consciousness, as being in the so-called subcortical centers of consciousness situated in the *interbrain* Similar symptoms, including hyperesthesia, have been described by Henry Head as accompanying lesions of the thalamus where the great subcortical relay station of the sensory tracts is situated The association of lesions in the interbrain with various affective responses to sensory impulses, such as fear, anxiety, rage, flight and defense reactions is well established (Tilney and Riley (99), Huber and Crosby (56), Herrick, (52) Demole (18) and others) As Tilney and Riley remark "Clinical evidence seems to be insistent that the thalamus is the center for affective tone," and "psychic processes representing a certain degree of consciousness may be carried on by the thalamus independent of the cerebral cortex These processes are probably limited to painful sensations The thalamic centers are chiefly concerned with affective experience" Huber and Crosby state

> The thalamus provides for the affective tone of impulses, and is a primary center involved in various types of emotional expression Normally, this center gives the emotional content to a given response The work of Head and Holmes indicates that the thalamus is closely connected with affective

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experience and with the whole range of pleasurable and painful qualities, which are undisturbed when lesions are confined to cortical centers alone

Herrick says

In certain diseased conditions where the thalamus is isolated from its cortical connections by destruction of the thalamic radiations the functions of the thalamus itself come into the foreground of the clinical picture In this "thalamic syndrome" pure affective experience is intensified The slightest stimulus may be extremely painful, but there is no intelligent analysis of the experience or localization of the stimulus It is sheer pain, uninterpreted and better expressed by "it hurts" than by "I feel a prick in my hand "

There can be little question that *the symptoms of group (a) and also of group (e) (general hyperesthesia) harmonize so well with disturbed function (irritation) of the thalamus as to make it a reasonable assumption that they originate in this center*, even had not our survey of the pathology shown that lesions, vascular and ganglionic, are pronounced and frequent in it Further, in relation to the point of entry and route of invasion, we may refer to the discussion of the anatomy of this region in relation to the olfactory paths and to Herrick's statement quoted on p 107

(b) There would appear to be as little doubt that *the disturbances of sleep* in poliomyelitis are due to involvement of the nervous mechanisms controlling sleep as there is in the case of lethargic encephalitis (to which in this respect poliomyelitis bears a rather striking resemblance) or of tumor The localization of the area dominating sleep has been thoroughly reviewed by L'Hermitte and Tournay (76) and is based mainly on clinical observations in brain tumors and lethargic encephalitis and on the striking experimental work of Demole (18) in cats Although there is some disagreement as to its total extent, the findings are in substantial agreement that the area responsible for the regulation of sleep and for the disturbances of sleep in disease is situated in the lowermost portion of the gray substance of the *hypothalamus* (tuber cinereum and its vicinity) (Demole) It will be seen, again, that this area is exactly in the path of the basal tracts descending directly from the olfactory lobes, and at a place where the lesions of poliomyelitis are even more marked and common than they are elsewhere in the basal ganglia

(c) *Disturbances of sympathetic function* Bard (8) has reviewed the evidence on central control of sympathetic functions and concludes that

> the diencephalic representation of the sympathetic system constitutes that dominant central mechanism the existence of which is so plainly implied by the tendency of the sympathetic nerves to discharge vigorously and as a whole under conditions of stress

The following sketch of the central representation of the sympathetic nervous system is suggested by the physiological evidence at hand The preganglionic neurones which have their origins in the lateral horns of the thoracic and lumbar segments of the cord are normally under the control of supraspinal influences This control may be exerted continually and so lead to a steady discharge of impulses to postganglionic neurones or it may become evident only when the controlling influence is set into action by circulatory, metabolic or reflex influences The tonic discharge is subject to both central excitation and inhibition Functionally similar groups of preganglionic fibers are normally under the control of their respective bulbar mechanisms, which suffice for the ordinary tonic and reflex sympathetic discharges Higher levels are not essential for their activity Superimposed upon these bulbospinal mechanisms is *a dominant mechanism located at the base of the diencephalon* and capable of causing a simultaneous discharge over the entire series of preganglionic neurones The various functional activities of the sympathetic nervous system certainly appear to have a neural basis of this sort

Huber, in his discussion of this paper, says of the pathways connecting this diencephalic sympathetic center with the periphery "The visceral efferent discharges have not as yet been definitely determined The main discharge-path appears to be through the periventricular system and thence to the dorsal tegmental nucleus and through the fasciculus of Schultze to the bulbar centers" This statement is cited with reference both to the pathways connecting with the olfactory tracts, already mentioned in the section of Anatomy, and to the pathways by which the advancing infection might pass from the hypothalamus to the medulla and lower

It appears that *the sympathetic manifestations of the initial phase of poliomyelitis may, and probably do, have their origin in the hypothalamus* in an area at the basis cranii closely adjoining the sleep

regulating center, where lesions are frequent and marked, and in the path of the outgoing olfactory tracts

(d) *Disturbances of the vomiting mechanism* The common symptom of loss of appetite has been included in this group on the basis of Dumpert's (21) work He concludes that both nausea and loss of appetite have the same origin and significance as vomiting Dumpert believes that all these disturbances are essentially due to circulatory changes mediated through a vasomotor center and represent an effort on the part of the controlling mechanism to divert blood from distant plethoric or hyperemic areas, such as the splanchnic bed If this hypothesis is correct it would imply a control on the part of the vegetative center in the diencephalon Until very recently, however, no center with a direct influence on the vomiting mechanism was known higher than that described by Hatcher and Weiss (51) in the sensory nucleus of the vagus in the floor of the fourth ventricle Cushing's (106) recent experiments, however, now point to the existence of an area in the hypothalamus near the third ventricle controlling various parasympathetic functions, including vomiting The injection of pituitrin into the third ventricle was promptly followed by retching and vomiting, along with other related symptoms Reasons have already been given why the early vomiting of poliomyelitis is not to be regarded as due to a local disturbance of the gastrointestinal tract Cushing's production of vomiting by a stimulus applied to the *hypothalamus,* an area known to be frequently and heavily involved in the pathology of poliomyelitis, is highly suggestive of the origin of the initial vomiting of the disease The gray matter in the floor of the fourth ventricle is also the seat of inflammatory lesions in many cases and it is not unlikely that vomiting may originate here, too, but perhaps at a slightly later period of the infection

(e) *Disturbances of sensation* These have been discussed under (a)

(f) *Headache* The headache of poliomyelitis is probably not ordinarily due to increased intracranial pressure In three of Draper's cases (36, first series, 6, 19, second series) with headache at the onset the pressure was normal In the first globulin was present in the fluid, without increase of cells, while in the other two the cells were increased It is highly probable that the headache is a manifestation of an acute inflammatory intracranial process (hyperemia?) but the exact mechanism of its production cannot be definitely stated

(g) *Fever* The localization of the center for the control of temperature is apparently well established in the hypothalamus The work up to 1930, as reviewed by Bard (8), is in essential agreement on the point, and recently Keller and Hare (62) who extirpated the hypothalamus in cats appear to have furnished conclusive proof of it They say "These observations indicate that the chief central mechanism controlling heat production is located in the hypothalamus, and that extirpation of this region releases the heat loss mechanism, located elsewhere, from coordinated control" That fever clinically observed in disease originates in this general area has long been believed (Hewlett (53)) Knowing the frequency of lesions in poliomyelitis, we may suppose that they, rather than some indirect or general toxic effect, are responsible for the fever which is almost, if not quite, invariable at the onset of the disease

It has been shown that *almost the entire symptomatology characteristic of the onset of poliomyelitis is traceable to the diencephalon, particularly the hypothalamus and thalamus* [10] The objection to ascribing them to lesions directly resulting from the presence of, and immediate reaction to, the virus itself in that area, may be made that similar symptoms accompany the onset of various general infections in which presumably no inflammatory disturbance is present there due to the direct effects of the causative microorganism The answer to this objection is twofold First, the clinical syndrome is, as has been

[10] Case 31 of the Rockefeller Monograph series affords further evidence of the localization of infection in the inferior region of the interbrain A boy of four and three quarter years showed at the onset, during an evening, headache and a little fever The next day he was feverish, very drowsy, vomited, and it was noted that he was unable to move his eyes so as to look downward He could close them and move them normally in other directions The pupils reacted to light and accommodation Photophobia was marked The knee jerks, when obtained, were active The superficial reflexes were active The Babinski was doubtful but the Oppenheim was positive The spinal fluid showed 320 cells and a slightly positive test for globulin No other paralysis, excepting a slight internal squint and loss of convergence developed

The paralysis of vertical gaze in this case was plainly due to involvement of the corpus subthalamicum (see Tilney and Riley, p 617) in which an aberrant portion of the pyramidal tract is represented, connecting with the corpus striatum and the oculomotor nuclei

At the same time, the rarity of such cases in poliomyelitis points to a tendency of the infection to continue in directly communicating tracts rather than to spread to their anatomical neighbors The visual and olfactory tracts, although closely adjoining each other in the interbrain and midbrain appear to have rather few interconnections

Draper's own cases therefore fail to bear out his conception of the disease, which is most clearly seen in his semidiagrammatic formulation on p 42 of his book, and which has taken such strong hold on clinicians in this country His conception of the disease is that it consists of two periods separated by greatly varying intervals During the first, the symptoms are variously those of fever, dullness, irritability, drowsiness, resentfulness, vomiting, etc and the fluid is "clear Pressure slight or greatly increased Amount increased Cells 0–5 Globulin 0–± or + " During the second phase, the characteristic neurological signs appear and the fluid then shows increased cells, strongly positive globulin test, pressure normal or increased

It would appear, on the contrary, that *the changes in the spinal fluid are quite independent of the presence or absence of the ordinary pathological neurological signs, and may be present when the clinical symptomatology, other than fever, is minimal* As has been said, the spinal fluid changes are undoubtedly secondary and hence subsequent to the actual invasion of the nervous tissue, but it is striking how early they may be present and marked

Summary of the first phase

It will be in better accord with the facts and probabilities of the case if we regard the first stage of acute poliomyelitis as that in which invasion of the virus is largely confined to the intracranial structures, especially the brain stem Indeed, this stage might be designated as predominantly the stage of interbrain symptoms In our classification it will for convenience be designated as the "cerebral" or "diencephalic" phase It is of historical interest to recall Redlich's (88) surmise, made 38 years ago·

> we therefore see that quite the same manifestations as we find in the spinal cord can also occur in other parts of the central nervous system This opens up the possibility that a part of the cerebral, manifestations which so often accompany the onset of poliomyelitis and which have hitherto usually been ascribed to general effects of the infection, are sequences of a local involvement of the brain

Second phase

Reference to table 8 of the symptoms following those of the very beginning of the manifest disease but preceding the appearance of paralysis brings clearly to light a definite change in the clinical picture While the symptoms most frequent in the first phase continue, indicating persistence of their underlying pathology, other symptoms and signs now occupy the foreground These are localized pains and tenderness (rather than general hyperesthesia), stiff neck, painfulness of the neck and spine to flexion In addition, ataxia and tremor, local weakness without paralysis become more frequent The physical examination reveals in a large proportion of cases increase of the tendon reflexes and pain to the Kernig maneuvre Medin's (79) report is particularly memorable for its account of the sensory manifestations

While most of these symptoms and signs are usually ascribed to "meningeal irritation" they differ in some esssential respects from those seen in ordinary meningitis, and it will be recalled that the arachnoid surfaces in poliomyelitis are not the seat of exudative deposits or lesions such as are seen in ordinary meningitis The authors of the Rockefeller Monograph made a clear distinction between the manifestations in the two types of disease, which was later enlarged upon by Draper (19), who says

> In acute poliomyelitis any manipulation which brings about anterior bending of the spine causes pain and, therefore, is resisted by the patient The resulting stiffening of the body has generally been loosely described as "stiff neck" or "Kernig's sign," but there is an essential difference between these reflex phenomena of meningeal irritation and the voluntary protection rigidity assumed by the patient with poliomyelitis to prevent anterior flexion of the spine This conscious effort is often carried to a moderate degree of opisthotonos, and is the cause of the unwillingness of children with this disease to be picked up and handled even by the mother
>
> This phenomenon may be present before any invasion of the meninges has occurred as shown by negative spinal findings We have suggested as an explanation for the sign that in flexing the spine anteriorly the intervertebral spinal ganglia are pulled upon If it be recalled that the virus has been found experimentally in the posterior spinal ganglia before meningeal invasion this suggestion for the mechanism of the spine sign receives

some support It is conceivable that the ganglia being the seat of inflammatory reaction may be unduly sensitive

"Pain," according to the Rockefeller Monograph (p 47),

in some form is a constant feature of the acute stage of poliomyelitis In general, three types are found, spontaneous pain, pain caused by manipulation, and tenderness to pressure of the muscles and nerve trunks These are not at all equally common Pain caused by passive motion is most frequent and seems to depend primarily upon anterior flexion of the spine we have been led to believe that the stiff neck of poliomyelitis differed from that of meningitis in being voluntary rather than reflex

Spontaneous pain sometimes occurs in poliomyelitis This is much less frequent than pain on manipulation Usually it follows the course of the nerves like a true neuritis It may be very severe Such pain may perhaps be more often present than is generally supposed, for it frequently requires much urging and even sharp prodding to make a child move an extremity which seems to be paralyzed, when in reality the muscles have power but are painful The third painful feature of acute poliomyelitis is the tenderness of muscles to pressure There is little doubt that this tenderness is in the muscles and is not a hyperesthesia of the skin, for rubbing the skin without pressing on the underlying muscles, or even pinching, causes no painful sensation

Under "Pathology" the frequency of lesions in the posterior horns of the cord, and in the intervertebral ganglia has been noted, as well as the experiments of Flexner and Amoss (32) which are those referred to in the quotation from Draper

It is curious and significant that the sensory disturbances in the acute phases, particularly the second, are of *pain*, whereas discriminative sensibility is apparently rarely, if ever, affected *Thermal sensibility*, with which pain is functionally and anatomically associated (Lissauer's and spinothalamic tracts) is also involved Muller (82) has an important note on this point He says

in the above mentioned older patients, a dissociated paralysis of sensation was definitely present, of such a sort that along with touch sensation the pain and temperature sensations were first and foremost weakened It was therefore the "posterior horn sensibility" in Strumpell's sense that was damaged, that is, those qualities of sensation which pass through the

incoming posterior root fibers to the posterior horn, make connection at just that point with ganglion cells and make their way upward in other neurons in the antero lateral tract area after decussation in the anterior commissure *This more or less elective injury to posterior horn sensibility* at the beginning of the disease is easy to understand in a "poliomyelitis posterior," and the pathologic-anatomic findings which show a frequent involvement of the posterior horns in fresh cases, speak throughout in favor of our view that such dullings of the sensations of temperature and pain in quite fresh cases of poliomyelitis are frequent Such disturbances of sensibility (particularly of the posterior horn type) have already been repeatedly described, e g , by Medin and Wickman In the literature it is reported that in such "poliomyelitis posterior," persistent sensory disturbances also occasionally occur

It would appear, therefore, that the sensory disturbances point not only to an irritation of the neurons conducting these sensations (as shown by spontaneous pains) but also—at least in some cases—to an actual interference with their conducting function

The tremor, muscular twitchings, weakness without paralysis and ataxia noted sometimes during this stage (and actually occurring much more frequently than is indicated by the figures from the two series here cited) are, in all probability, early irritative signs of the beginning onslaught on the anterior horn cells and, perhaps, those of the column of Clarke Their frequency before the period of actual flaccid paralysis is a matter of common experience and is also shown nearly always by experimentally infected monkeys

Summary of the second phase

In general, the dominant symptoms of the second phase of poliomyelitis are sensory and point to (*a*) involvement of the posterior spinal ganglia, (*b*) involvement of the posterior horns particularly those portions implicated in the conduction of the sensations of pain (and temperature) The peculiar significance of such involvements will be presently discussed

For these reasons, the second stage might be designated the "lower sensory stage," and is regarded as being in essence the stage of "poliomyelitis posterior " Signs of irritation of the lower motor neurons supply evidence of transition to the next phase

Third phase (stage of paralysis)

As contrasted with the marked variability, in respect to the individual cases, of other clinical phenomena of acute poliomyelitis, one manifestation is nearly constant the fact that when it occurs at all, *the paralysis is a sequel to other symptoms and signs*, and rarely if ever comes first in the chronology of any case With increasing clinical attention to the early manifestations of the disease, "morning paralysis" has almost disappeared from modern case records The chronological position of paralysis completes the demonstration of a peculiar and orderly sequence of disturbances of the central nervous system which it is the purpose of this paper to make *Involvement of the anterior cells of the spinal cord is, in the ordinary type of case* (the encephalitic cases constitute a separate category), *the last and culminating development of the disease* It will be seen from table 10 that at the time of appearance of paralysis, the symptoms of the first and second stages are still present, they, however, regress rapidly in cases going on to recovery, and frequently the paralysis itself, reaching its maximum within a brief period, also regresses to a varying extent

Since in nearly all cases, disturbances of the lower portions of the sensory tracts precede paralysis, *it is a reasonable inference that invasion of the anterior horn cells has its immediate source in infection either of the posterior horn cells or of the intervertebral ganglia or both* Reference to the section on Anatomy will show the multitude of paths, intra- and intersegmental, available for such a route of attack The manifestly far greater vulnerability of the anterior horn cells to lethal effects from the virus of poliomyelitis is in itself an argument, taken in conjunction with the clinical sequences of the disease, for an attack by such routes

Fourth phase Stage of recovery

For a considerable period in a certain proportion of cases, cerebral and sensory disturbances persist They are to be sure rarely permanent The Rockefeller Monograph (86) mentions that "in some cases there is a nervous apprehension which lasts for weeks " Muller (82) mentions the persistence of psychic changes along with disturbances of sleep, especially in older children, for weeks or months There was a notable lessening of what he calls their previous "geistige

Frische" and vivacity, a marked fearfulness and anxiety with a tendency to weeping, palpitation of the heart and trembling In one girl there was, according to the mother, a decline in intellectual capacity

The persistence of tenderness in affected extremities, in the muscles as well as along the nerve trunks, for weeks or more is too well known to require special documentation Medin's (79) report in which unusual severity and persistence of neuritis are described is of special interest

Paralyses diminish in severity and extent in varying degrees in nearly all patients surviving the acute stage, even to the point of almost complete recovery of function Such improvement varies also in rate Most observers are in accord with Wickman (104) who says that while the majority of complete recoveries are doubtless completed in the first half year, they are not so rare in the second half year, and occasionally even later The lateness and gradualness with which improvement may occur suggests that the impaired function of the ganglion cells is not due to pressure from edema and hyperemia, as has so often been asserted, but to an actual infection of cells which are damaged to less than a lethal extent by invading virus The theory of nerve cell damage from pressure never stood on a very firm basis since it has been repeatedly observed (Rissler, (90) Draper (1)) that perfectly normal ganglion cells may be found in intensely inflamed and infiltrated areas, side by side with damaged or even necrotic cells, while in certain areas such as the medulla the inflammatory process may be very intense without producing degeneration of the cells or even detectible disturbance of their functions

The *distribution of the residual paralyses* of poliomyelitis supplies interesting information, not so clearly manifest, either from the symptomatology or from the pathology, during the acute stages of the disease Even then, unequal involvement of the two sides of the body and, of course, great differences in involvement of different levels of the body are apparent, both in the sensory and in the motor fields With the subsidence of acute symptoms and progressive recovery, the distribution of residual palsies becomes more sharply defined and has, I believe, a certain significance in respect to Fairbrother and Hurst's (26) thesis of spread of virus by nerve tracts The most suitable compilation of case reports for the purpose is that of Lovett and Lucas

(77), with a rearrangement of the data as summarized by them (table 12)

To the manifest and quite striking tendency to unilaterality in this table (notably more marked in the cervical than in the lumbar groups),

TABLE 12

Distribution of residual paralyses, Lovett and Lucas

Original table of Lovett and Lucas		
Both legs	130	
Right leg	216	
Left leg	239	
Right arm	5	
Left arm	5	
Both arms alone	0	
All four extremities	3	
Arm and leg, same side	15	
Arm and leg, opposite side	7	
One arm, both legs	2	
Abdomen with other paralysis	6	
Analysis of figures		
Arm involvements		
Unilateral	34	(91 8%)
Bilateral†	3	(8 2%)
Total cases	37	
Leg involvements		
Unilateral	477	(77 9%)
Bilateral	135	(22 1%)
Total cases	612	
Arm and/or leg involvement		
Unilateral at given level	487	(78 2%)
Bilateral at given level	135	(21 8%)
Total cases	622*	

* Abdominal cases omitted, in these the side of involvement is not given

† All three were cases in which all four extremities were involved

the practically uniform unilaterality of bulbar paralyses (Rockefeller Monograph (86)) may be added Its significance would appear to be in indicating that while, during the acute stage of poliomyelitis,

virus is doubtless descending along many pathways, its main, its heaviest invasion and attack follow only a few, and hence its lethal effects, without possibility of recovery, are restricted to cells which receive an overwhelming amount of virus

The mere fact of recovery from poliomyelitis, the fact that maximum paralysis occurs soon after initial paralysis in the average case, that then the various manifestations of the disease, save such as are due to actual destruction of ganglion cells, regress and disappear, strongly indicates *that the virus of the disease is after all poorly adapted to survival in man, that its hold is precarious, and perhaps that the defenses of the body against it are more effective than we are inclined to think*

VI THE ROUTE OF PROPAGATION OF VIRUS IN THE HUMAN DISEASE INTEGRATION OF THE ANATOMICAL, PATHOLOGICAL, EXPERIMENTAL AND CLINICAL DATA

A consideration of the clinical manifestations of poliomyelitis in the light of the probable point of entry, the interconnections of various nerve tracts, the distribution of the lesions, the function of the various portions of the central nervous system found to be particularly involved, as outlined in the preceding sections, logically leads us to the inference that the disease in its common form has a definite and orderly mode of progression within the central nervous system up to its climax of lower motor neuron paralysis, and permits us, tentatively at least, to conclude that the invading virus follows, as a rule, fairly well defined main routes of travel

The accompanying diagram (fig 4) shows the conception of these routes that has been developed in the preceding sections The primary focus of infection in the olfactory bulb, after entrance of virus through the nasal mucosa and olfactory nerves, leads to infection of the hypothalamic area and perhaps of the olfactory cortex The descent of infection from both these areas leads to essentially the same centers in the thalamus and midbrain The main pathway then leads from the thalamus downwards through the spinothalamic tract to the posterior horns, whence infection reaches the dorsal root ganglia and anterior horns The anterior horns, with the columns of Clarke and the anterolateral gray matter are again exposed to infection from their connections with the dorsal root ganglia

The selection of this as the main route is based partly on the results of experimental work, which has given partial confirmation of it,

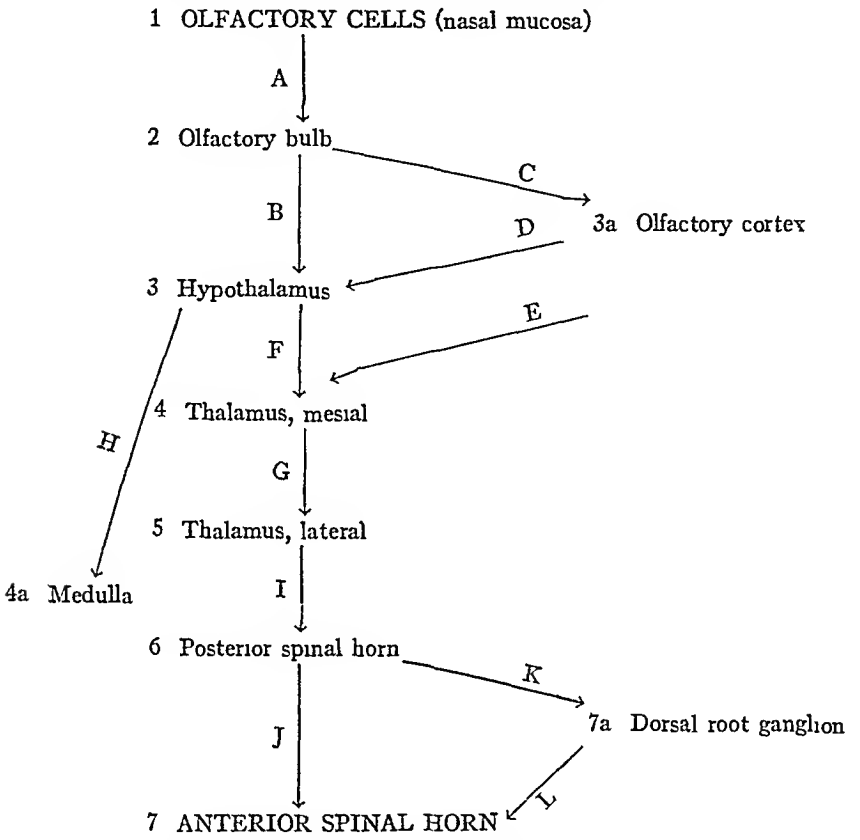

FIG 4 MAIN ROUTES OF PROPAGATION OF VIRUS

Omitted from this list are several centers not regarded as in the main route of propagation but nevertheless frequently affected the midbrain (especially the dorsal tegmental nucleus of Gudden), connected with the hypothalamus and mesial thalamic nuclei, the columns of Clarke and the anterolateral portion of the spinal gray matter, connected with the dorsal root ganglia The commissural connections with corresponding areas of the opposite side are also omitted The connecting tracts indicated by capital letters are as follows *A*, olfactory nerve *B*, basal olfactory bundle *C*, olfactory radiations and intermediary nuclei (anterior perforated space, amygdaloid nucleus, fornix, etc) *D*, fornix to mamillary body *E*, fornix and stria medullaris thalami *F*, bundle of Vicq d'Azyr, *G*, intercalary fibers *H*, connections mainly through reticular formation (sympathetic and parasympathetic adjustor system) *I*, spinothalamic tract *J*, intercalary fibers *K*, Lissauer's tract *L*, axons of dorsal root ganglion cells mediating direct spinal reflex

partly on the distribution of the lesions in human cases, and partly on the character and order of development of the clinical symptoms The progression from an initial stage of hypothalamic and thalamic

symptoms to a second stage of posterior horn and dorsal root ganglion symptoms, and then to a third stage of anterior disturbance is clearly marked in many cases Sometimes the first stage is slight or fails to be observed In the so-called abortive cases, the third stage is absent or slight But in practically all cases of the ordinary form of poliomyelitis with paralysis, the second and third stages occur in the order named, the second consisting of the usual preparalytic symptoms and signs Because of this order of progression (and because of the detection of infection in experimental animals in the dorsal root ganglia before paralysis) the spinothalamic tract has been selected in the present scheme as the main route of descent of infection from the brain to the cord in preference to one or more of the motor tracts that descend from above to make direct synaptic connections with the anterior horns

A second, collateral pathway leading from the hypothalamus to the medulla is represented in the diagram as ending there This is assumed to consist of the tracts of the reticular formation, a structure probably containing various vegetative centers and pathways and having connections with the motor cells of the bulb and cord Lesions in the reticular formation, especially in the medulla are frequent and pronounced, according to Harbitz and Scheel With Gebhardt I have detected virus in the medulla on the fifth day of the incubation period in experimental animals at a time when the only other places where it could be found were the olfactory bulb and hypothalamus Moreover, transient bulbar symptoms are not uncommon in the earlier phases of the human disease However, bulbar palsies are relatively infrequent and other bulbar disturbances rarely persist Moreover, the fact that the descending reticulospinal tracts probably form synapses with the motor rather than the sensory cells of the cord creates the same objection to these as to other descending motor tracts as the main routes of infection

Finally, the chief bulbo-spinal *sensory* pathways—the tracts of Goll and Burdach—have not been included in the scheme because their nuclei (N gracilis and N cuneatus) apparently escape in most cases and the type of sensibility which they convey is not conspicuously disturbed in the disease

The main route for the propagation of virus from the outer world

to the anterior horns of the cord is therefore inferred to be as follows *olfactory nerve endings in the mucus of the nasal mucosa through the axons of the olfactory nerves to the olfactory bulb, through the olfactory tracts to the hypothalamus, through connecting tracts and fibers (bundle of Vicq d'Azyr, etc) to the thalamus, through the spinothalamic tract to the posterior horns of the spinal cord, through connector fibers to the anterior horns and dorsal root ganglia, from the dorsal root ganglia through connector fibers to the anterior horns* A collateral pathway leads from the hypothalamus to the medulla, mainly through the formatio reticularis

Such a route corresponds with some accuracy with the character of the symptoms of the disease and with the order in which they develop, as well as with the distribution of the lesions, the probable portals of entry, and with the anatomy of the tracts of the central nervous system as they connect with the olfactory bulb at one end and with the anterior gray matter of the cord at the other It should be noted, however, that the route as outlined is suggested as the *chief* pathway, not as the only possible one The alternative possibilities are many nor must it not be supposed that the virus is ever limited to spread along such restricted channels as have been described The controlling factors in holding the advancing infection to a particular route appear to be, in the main *first, direct anatomical connections between ganglion cell centers, second, the suitability of the cellular material in these centers for implantation and multiplication of the virus* Fairbrother and Hurst have shown how virus inoculated in cerebral cortex dies out and leaves the cells there unchanged while, simultaneously, it has passed along to other centers which are more vulnerable and, presumably better adapted to act as host to it

A truer picture of the advancing infection than that of one anatomically limited to a single series of nerve tracts would be somewhat as follows From its initial focus, the olfactory bulb, virus begins during the period of incubation to travel in many directions open to it through synaptic connections In most of these, it will encounter conditions such as Fairbrother and Hurst have shown to exist in the cerebral cortex, that are unfavorable to its multiplication and survival In others it will obtain but a transient foothold (medulla) Only along those routes that lead it to areas best suited for its survival (gray matter of the cord) will it continue to multiply and progress and

produce its principal manifestations This process has, of course, the effect of a selected route of propagation, even though in a stricter sense, it is merely a process of general diffusion and limitation of survival to certain restricted areas

The *rate* at which the disease progresses from one point to another is subject to the most extraordinary variations In some cases it is more than a week from the appearance of the first symptoms before paralysis occurs In many instances, paralysis never occurs In many cases—a phenomenon to be presently discussed—there are intervals of interrupted progress In a considerable number of cases, progress is extremely rapid Nevertheless, it is rare to find a case in which characteristic symptoms, signs and alterations of the spinal fluid cannot be detected before the appearance of paralysis

These variations in rate of progress suggest variations in the rate and degree of formation of the foci of early infection in the central nervous system, whether in the olfactory bulb or a step or two lower in the descending pathways, whence the virus descends to more susceptible areas, in the slow or mild cases, trickling through, as it were, in severer, more fulminant cases, flooding downward in overwhelming amounts, almost unchecked

The analogy to water working its way through a more or less porous barrier at rates varying with the amount or head at the source and with the degree and quality of obstruction present, following the lines of least resistance, may perhaps be carried a little further If the obstacles against its advance are sufficient, penetration will be slight and its progress will be halted If they are considerable but not quite sufficient, its progress may be slow or only temporarily halted This brings us to the consideration of one of the most marked peculiarities of poliomyelitis the tendency to interruptions in its course

VII THE PHENOMENON OF "HALTING", ITS RELATION TO VARIANT FORMS OF THE DISEASE AND TO THE MODE OF PROPAGATION OF THE VIRUS

One of the major characteristics of acute poliomyelitis, the significance and importance of which have been confused and insufficiently appreciated in the past, is the peculiar manner in which it tends to halt for a varying period at one time or another in its

course, then, after an interval of symptomatic silence, again to advance, and in a very considerable proportion of cases, to cease again without ever reaching the climax of paralysis Most of the variant forms of the disease illustrate this tendency to interrupted progress, indeed, it is detectible in nearly all of the "typical" cases in which the infection is not fulminant and overwhelming Intervals vary from a few hours to many days, and sometimes much longer More than one may occur They may appear at any stage of the disease Occasionally, mild symptoms may continue from one period to another The phenomenon is best demonstrated by a consideration of certain types of cases

Abortive cases

Of the 115 cases of the two series (Rockefeller Monograph and Draper), 40 (34 8 per cent) never developed paralysis The ratio of abortive to paralytic cases doubtless varies considerably in different epidemics and has been variously estimated (see Wickman (104)), but it is undoubtedly high and probably of the general order of 1 1 The point to which attention is particularly called is that, as the Rockefeller Monograph (86) states, (p 79) "*there is little difference between the symptoms of the abortive cases and the prodromal symptoms of cases which become paralyzed*" *Moreover, the changes in the spinal fluid are as constant and as characteristic.* In the 40 cases, all but three showed increased cells at the first puncture, and these three showed globulin Since such changes constitute indisputable evidence of the presence of lesions in the central nervous system, *the assumption that the abortive cases are those with "systemic" infection, rather than with central nervous infection is wholly unwarranted and, indeed, contradicted by the facts*

Occasionally the disease appears to stop before entering the second phase Thus, Draper's case 21 (first series) showed nothing more than fever, slight headache, and constipation and, three days later languor The physical examination was negative, but the spinal fluid was under moderate tension and contained 200 cells Nearly all, however, run into the second phase with well marked sensory symptoms and signs (spontaneous pains) local tenderness, pain on flexion of neck or back) and, as a rule, also increased knee jerks The spinal fluid in every

case showed pathological changes, increased cells at the first count in all but three and in these the test for globulin was positive In a few instances transient localized weakness indicated that the disease had passed just to the third phase before stopping Ten of the cases showed the "dromedary phenomenon"

A summary of the onset symptoms and signs in this group of cases shows the identity of the picture with that in the paralytic group, and its essentially nervous character (table 13)

The abortive cases are plainly those in which the poliomyelitic infection of the central nervous system is interrupted during the first or second phase, or both, and fails to advance beyond the latter

TABLE 13

Abortive group (40 cases), Rockefeller Monograph and Draper

Fever	28
Drowsiness (9), apathy (5)	14*
Headache	13*
Restlessness/irritability	10*
Vomiting (9), nausea (1)	10*
Constipation	6
Malaise and vague symptoms	7
Localized pain, tenderness or hyperesthesia	4*
Stiff or tender neck	4*
Tender spine	2*
Diarrhea	4
Sore throat	3
Loss of appetite	3

To these we may add a transitional form in which the disease advances just to the beginning of the third phase, produces a transient weakness of one or another group of muscles, then stops and leaves no residual paralysis Case 23 (Draper, second series) is an example of this

Dramedary cases

Draper (19), who introduced this term, used it to illustrate the theory that the disease is divisible into an initial period (first "hump") of general infection and, after an appreciable interval of symptomatic silence, varying from a few hours to a week or more, by a period of infection of the central nervous system (second "hump") A sum-

mary of the symptoms of the first and second "humps" in the 42 cases of his book and the Rockefeller Monograph with this phenomenon, however, shows again the same preponderantly nervous character of the symptoms of the first phase, and the fact that the second phase shows the same symptoms with marked increase in sensory manifestations that we have noted as characteristic of the disease in general (table 14)

TABLE 14

Dromedary group (42 cases), Rockefeller Monograph and Draper

	FIRST HUMP		SECOND HUMP	
	Number	Per cent of cases	Number	Per cent of cases
Fever	31	73 8	31	73 8
Vomiting	14*	33 3	11*	26 2
Vague	10	23 8	2	4 8
Headache	5*	11 9	*16*†	*38 1*
Constipation	5	11 9	4	9 5
Sore throat, tonsillitis	5	11 9	0	
Drowsiness	4*	9 5	7*	16 7
Apathy, quiet, "dopey"	4*	9 5	5*	11 9
Restlessness, irritability	4*	9 5	6*	14 3
Pain, tenderness, hyperesthesia	3*	7 1	*17*†	*40 5*
Diarrhea	3	7 1	1	2 4
Twitching	1*	2 4	3*	7 1
Weakness (without paralysis)	0		4*	9 5
Ataxia, stupor, wild behavior, each	0		1*	2 4

† These symptoms show a striking increase during the second "hump" Cf table 8

In two instances, the period intervening between the two "humps" was not quite normal, since drowsiness and headache respectively persisted In four cases (4, first series, 3, 9, 16, second series), the symptoms initiating both "humps" were identical While spinal puncture was done during the first "hump" in only three cases, globulin was present in two of them and was not tested for in the third

If, as has been suggested, the chief channel through which infection descends from the interbrain (first phase) to the posterior portion of the cord (second phase) is the spinothalamic tract, the great length of uninterrupted nerve fibers in it may offer an anatomical explana-

tion of the considerable period of symptomatic silence so frequently occurring between the first and second phases of the disease, for it is to be supposed that the virus produces symptoms only when it has reached and infected the cell bodies themselves The simultaneous affection of numbers of these cells in this way may be responsible for the sudden and "explosive" appearance of second phase symptoms

Cases with advancing paralysis

To this group belong most of the fatal cases, excepting those in which the disease appears to attack, suddenly and overwhelmingly, almost the entire central nervous system at one blow In a certain proportion of cases, paralysis first affects the higher portions of the bulbospinal axis, halts for a varying period and then descends to affect the lower portions, in others (Landry type) the progressing paralysis runs in the opposite direction In these the tendency to a halt before the advance is resumed has been noted by Peabody, Draper and Dochez (86), who say (p 69) "In the fatal cases, then, as well as in those that recover, there is usually a pause after the acute onset of the paralysis There may be one or two days without any definite increase in paralysis "

In cases of this kind, axonal spread of virus from infected motor neurons to others previously uninfected is manifest and the associated tendency to interruption is again clear-cut

Subclinical poliomyelitis

Strictly speaking, this is a hypothetical entity, postulated in explanation of the specific immunity known to exist in many persons who have never had the disease in recognizable form The difference between rural and urban populations shown by the notably greater incidence of such immunity in urban adults, with their greater opportunities for exposure as compared with rural dwellers (Aycock and Kramer (5)) is perhaps the best evidence at present available for the actual occurrence of cases of subclinical infection It is improbable that mere contact without infection is sufficient to produce the immunity, and it is obvious that an infection of the nervous system, such as I assume poliomyelitis always to be, must have ceased very early in its course to avoid overt manifestations If this is true, the

subclinical form of poliomyelitis is another and rather striking example of the phenomenon of "halting" It may be conjectured that the infection progresses in these cases no further than the olfactory cells of the nasal mucosa or than, at the most, the olfactory bulb It would appear likely that so abortive an infection must occur in individuals possessed of good powers of forming and rapidly mobilizing specific antibodies

Relapses and second attacks

Francis and Moncreiff (49) reviewed the literature on this subject and reported a case—the longest interval on record—in which the second attack followed the first by fifteen years Their paper shows that second attacks may occur at intervals ranging all the way from a few weeks to many years after the first In one instance cited by them (Ballet and Dutil) there were even three attacks (at the ages of 3, 12 and 14 years) Still (96) has more recently listed the cases (nine altogether, including one of his own) in which second attacks occurred after the interval of two years which Still selects as the criterion of second infection as distinguished from re-infection [11] While Still's criterion of two years appears rather arbitrary, his contention that relapses after relatively short intervals are due to a lighting up of the original infection appears reasonable, and in harmony with the conception of a disease that tends to advance by fits and starts It is, therefore, probable that the "halt" may extend over a considerable period of time and still lack finality

Summary We may sum up the observations in the preceding paragraphs in the statement that the poliomyelitic infection of the central nervous system in man shows *a marked and characteristic tendency to come spontaneously to a stop, temporarily for greatly varying periods, or permanently, anywhere in its course* It might seem *a priori* almost inevitable that a virus such as that of poliomyelitis, once lodged in tissues to which it is adapted, with so great a profusion of communicating channels as are at its disposal, would run its course unchecked until every part of the central nervous system were attacked and destroyed, or, if we assume a particular predilection or adaptation

[11] The possibility of a second attack from infection by a different strain of virus is raised by the recent report of Burnet and MacNamara (9)

to certain specialized groups or types of cells, such as those of the anterior spinal horns, that it should attack and destroy all of these Yet half of the patients never develop paralysis at all, and of those that do four-fifths or so show so limited and restricted an involvement as to be compatible with survival, many with residual loss of but one or a few groups of motor cells

The significance and importance of the phenomenon of "halting" are that it indicates clearly the presence of conditions or mechanisms in man[12] favoring spontaneous recovery from poliomyelitic infection, and it is to these that we must look for such hope of artificial prevention of paralysis as may be possible after infection has occurred Hence, while the explanations offered must at present be to a large extent speculative, the effort to understand these favoring conditions and mechanisms is of the greatest importance

VIII CONDITIONS FAVORING RECOVERY

First of all, we may imagine that the adaptation of the virus to human tissues is relatively slight and tenuous, its powers of survival relatively poor It is known that its survival in any tissues other than the nervous is very brief and even within the central nervous system, the observations of Fairbrother and Hurst (26) show that it dies out rapidly in the cerebral cortex at the very time that it is becoming implanted and is multiplying in the medulla and cord Such a phenomenon cannot be explained entirely on the basis of a general defensive reaction on the part of the body, and must be due in some degree to properties of the virus itself The relative importance of this factor—limited capacity for survival of the virus—cannot at present be accurately appraised, but it may well be considerable

That great variations in this capacity for survival (virulence) of different strains of virus exist is well known in respect to infection in the monkey, and that the same is true for man can hardly be doubted The demonstration of periodicity in virulence for a single strain has already been noted

The body itself possesses potential or actual specific defenses, of which the humoral virucidal (neutralizing) antibodies are the best

[12] The same is true to a vastly less degree of the monkey in which infection without paralysis and death is very exceptional

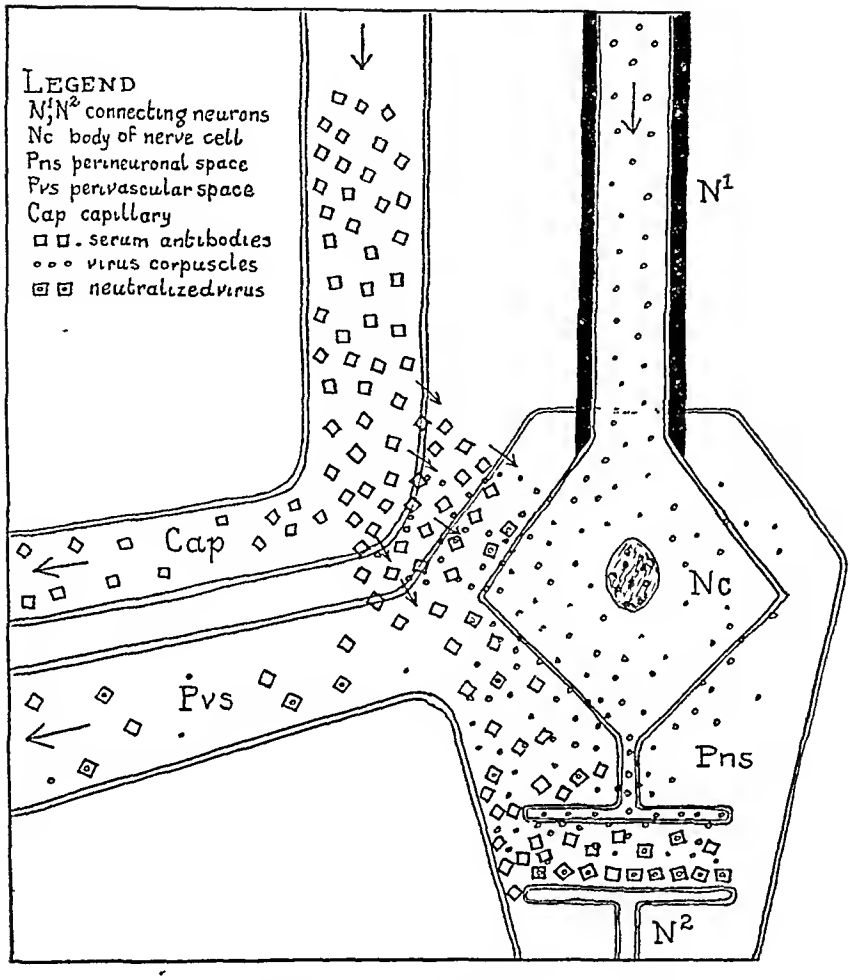

FIG 5 DIAGRAM ILLUSTRATING THE INVASION BY VIRUS AND ITS HYPOTHETICAL BLOCKADE BY NEUTRALIZATION

Virus is pictured as descending through neuron N^1 into and out of the nerve cell into the perineuronal space and the synapse with neuron N^2 below Simultaneously, under the effect of the invasion which causes increased endothelial permeability, specific antibodies escape from the blood capillary into the tissue spaces and the perineuronal and perivascular spaces, meet and neutralize the virus Between the terminals of the two neurons in the synaptic space, a solid wall of antibody has met and neutralized the virus and prevented its passage into neuron N^2 Serum antibodies, neutralized virus, and a small amount of unneutralized virus are passing out through the perivascular space, whence they will be discharged into the subarachnoid space The myelin sheath is represented as impermeable

The emigration of small cells (lymphocytes) may be imagined as following essentially the same channels as the antibodies in the diagram, except that the majority reach the perivascular spaces, and only a few the perineuronal spaces It would seem possible that their function may be somewhat similar, to remove virus that has escaped from infected cells

It is clear that if the perivascular spaces were unimpeded and the direction of the current in them reversed, antibodies introduced into the subarachnoid space would have a direct route to the infected synaptic area and perineuronal space The difficulties encountered are discussed in the text

known and most thoroughly studied They will be discussed in greater detail under "Treatment" They are detectible in the blood of about four-fifths of urban adults (5, 94) and a perhaps somewhat smaller but still very large proportion of convalescents from the disease at all ages (94) How rapidly they can be formed anew or mobilized to effective concentrations in the presence of actual infection is not known The actual mechanism by which they may reach, attack and halt the virus in its progress is also not known This is a critical consideration, however, and speculation on the point may therefore be permitted

Assuming axonal propagation to be correct, it may be supposed that the virus during its passage through the myelinated nerve fiber is confined within an impermeable tube, inaccessible to the body fluids Escaping from the nerve cell, however, it must for a time lie free in the synaptic area, and the surrounding tissue spaces, where it must come in contact with the tissue fluids derived from the blood stream It is at this time, too, that it probably excites the various phenomena of inflammation—hyperemia, edema, emigration of small cells into the perivascular spaces and the tissues themselves Providing neutralizing antibodies are present or can be mobilized in the circulating blood, they may be presumed to escape into the tissues at such points of inflammation and increased vascular permeability and thus come in contact with the invading virus [13] Depending on the resultant and relative concentrations of virus and antibody at and near the synaptic area, the former will either survive to pass on into the next neuron, or will be killed and so fail to advance The defense of the body against the advancing infection in poliomyelitis, therefore resolves itself into a series of local combats at the synapses, the outcome of which in each case depends on *relative* concentrations of virus and antibody [14]

[13] Under normal conditions, protein substances (to which humoral antibodies belong or are closely attached) probably escape in small amounts from the blood capillaries into the tissues Under pathological conditions of inflammation, the vascular permeability is altered to permit their escape in greater quantities In poliomyelitis, we have direct proof of this from the presence of notable amounts of globulin in the cerebrospinal fluid, even at a very early, prepiralytic stage of the infection

[14] Up to the present this hypothesis has no experimental basis, since in the monkey the infection, once established, appears to run its full course quite unmodified by the administration of serum Abortive cases, so common in man, are extremely rare in the experi

Using such an hypothesis we may picture the advance of the infection in a typical case somewhat as follows from an initial focus in the upper part of the central nervous system small amounts of virus begin to dribble downwards through the axons to the next relay point, here they invade and multiply in the cell bodies and produce corresponding symptoms, varying in intensity with the degree and extent of the damage produced in the cells and with the degree and extent of the secondary inflammatory reaction that follows when virus escapes into the adjoining tissue spaces If at this point the defensive forces are wholly adequate, the infection will go no further, and we must suppose that frequently this is the case (abortive cases); in other instances, the invasion is halted for a time or in the majority of synapses but after a time or at a few points the amount of virus formed by multiplication within the cells will overcome the defense, and so be free to pass along the whole length of the axis cylinder of the next neuron before it again has to encounter and be subject to adverse forces, where the conditions will be like those at the previous relay save for the increasing vulnerability of the cells in the lower portions of the bulbospinal axis The disease may thus be halted at any point or may go on indefinitely up to the time of death The fact that the descent of virus from one relay to the next is along only part of the channels potentially open to it, and so indicates a blocking of its progress at most of the latter, is shown by the tendency to follow decussating paths evidenced by the one-sidedness of the residual lesions.

That the lymphocytes which form so conspicuous a part of the secondary inflammatory picture have viricidal or other defensive properties is possible but at present unknown

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mentally infected animal The difference between the experimental disease in the monkey and the untreated natural disease in man is, however, very striking since in man abortive cases and other instances of interrupted progress of the infection are common, and I cannot, at present, think of any other possible explanation for them than the one here offered, or that the virus dies out in human nerve tissue before it finds a suitable kind of ganglion cell for its survival and multiplication The latter may, of course, be the correct explanation or even a combination of both, but I am much impressed with the fact that in the majority of abortive cases, the signs of posterior ganglion and horn disturbance are evident and that, therefore, the infection is already but one neuronal step and a distance of a few millimeters from the highly susceptible anterior horn cells

IX TREATMENT

The foregoing representation of the mode of propagation of the virus of poliomyelitis through the nervous tissues and the conditions under which it comes in contact with the circulating antibodies has been made with special reference to a consideration of treatment and more particularly of an attempted appraisal of the potentialities of treatment and the manner in which these potentialities can most effectively be utilized

Despite the large number of encouraging reports to be found in the literature, it cannot be said that by critical standards any one of them is wholly convincing or conclusive Kellogg's thoughtful paper brings out clearly the possible errors that may have arisen from data on the fatality rate and incidence of paralysis in case series not studied by the method of alternate controls Kellogg, while ending his discussion on a somewhat optimistic key, leaves the question of the value of convalescent serum open as at present unproved

The studies of Aycock and his associates (7) though perhaps not entirely conclusive, are nevertheless of special interest, in that an exhaustive anatomical survey was made of the various skeletal muscle groups, after recovery, to determine even the slightest degrees of residual paralysis Five hundred eighty-seven patients were thus examined, of whom 105 were treated in the preparalytic stage with convalescent serum, and 482 recovered without treatment On an arbitrary scale of 530 (maximum total paralysis) the treated patients showed an average of 19 0 paralysis, and the untreated, 63 6 In another tabulation, 71, or 61 2 per cent, of 116 treated patients, however, showed some degree of paralysis The treatment was apparently energetic (intravenous and intrathecal) and as thorough as in other reported series The studies therefore suggest that in other series, minor degrees of paralysis had escaped detection and that many cases, reported as cured, had in fact some residual paralysis Thus, while not wholly conclusive, the evidence tends to show that energetic serum treatment may to a considerable extent block the progress of the infection

With the picture before us of the mode of advance by infiltration of the virus within the central nervous system from one axon to

another and the possibility of neutralizing it at the synapses by supplying the surrounding tissues with virucidal antibodies, such an outcome as that reported by Aycock and his associates is readily understood, since it is to be expected that even at the time of serum administration virus had already penetrated, in a few places, into the motor cells where it would escape the action of antibodies in the tissue fluids, and thus be free to produce its characteristic degenerative effects

Only on the hypothesis of systemic, extranervous infection in the preparalytic stage of poliomyelitis—such as must be regarded as disproved—*could a different result be expected, with a complete neutralization* of virus in the blood stream and lymphatic system before invasion of the central nervous system Such a hope must be abandoned Nevertheless, there is sound reason for believing that the potential value of specifically immune serum in poliomyelitis has not yet been generally attained in practice, less for lack of potent serum than for failure to observe the principles, already understood, of effective serum therapy in general The methods in general use may properly be criticized in the respect to the serum used, the amounts employed, and the manner of administration

Convalescent serum, which has been almost exclusively used in this country, has not only as a rule been untested and unstandardized, but there is some reason to believe it to be ordinarily of rather low specific potency The striking work of Shaughnessy, Harmon and Gordon (94) showed that the assumption of a uniformly superior neutralizing power in the serum of patients who have recovered, even recently, from the overt disease is mistaken, and that in fact such serum more frequently failed to contain demonstrable antibodies than that of persons without a history of poliomyelitis Moreover, they found the highest potencies in persons of the latter category, two of whom showed the extraordinary neutralizing titer of 1 200 Aycock and Kramer's report (5) shows that even pooled convalescent serum occasionally failed to protect monkeys Faber (23) called attention to the desirability of using serum that had been tested and found to contain immune substances in sufficient concentration, and to the fact that it was feasible to test transfusion donors In his study the majority were found to be immune, and a few, highly so (up to 1 60)

With this exception, all reports on serum treatment have been based on untested serum from convalescents, the therapeutic results from which might be expected *a priori* to be similar to those from the treatment of diphtheria with serum of an unknown, varying and sometimes low content of antitoxin units

Since the publication of the paper by Shaw, Thelander and Fleischner (95), advocating intramuscular injection, this or intravenous administration of serum has come into greater use, especially in the West Many, perhaps a majority of, physicians, however, continue to prefer the intrathecal to the blood-vascular route Aycock, Luther and Kramer (6) advocate a combination of the two Now, while the vascular route may have been proposed on the basis of the erroneous hypothesis that poliomyelitis is a blood-borne disease, there is nevertheless good reason to believe that it is not only the route of choice, but *the only route which promises to reach the seat of the disease with any certainty for any considerable length of time*

Against the intrathecal route, which has been preferred by so many clinicians, there are important objections that apparently have been little appreciated This method is based on the belief that the chief route of infection is by passage through the choroid plexus and the meninges from the blood and into the subarachnoid space, and that foreign substances introduced into the subarachnoid space will readily and freely pass from the latter into the perivascular and perineuronal spaces The erroneous nature of both these postulates has already been indicated, but the second may be discussed further in detail As has been stated, *the normal direction of flow of fluids in the nervous tissue spaces is from the perineuronal and perivascular spaces towards and into the subarachnoid space (101), and any serum injected into the latter could only enter the former by regurgitation, that is, by reversal of the normal direction of flow* That under abnormal conditions, such as are induced by intravenous injection of strong hypertonic solutions, by anemia produced by ligation of the supplying arteries or by increased intrathecal pressure, a reversal of flow of cerebrospinal fluid may actually occur even into the perineuronal spaces has been shown by Weed (102), and by Mott (81) To what extent it is possible to take advantage in practice of such regurgitation is, however, a debatable question

Landis has shown that (in the skin) the capillary pressure at the arterial end is about 32 mm Hg (about 435 mm H_2O) Fahr, Kerkhof and Conklin (24), have shown that the average osmotic pressure of the blood is about 21 mm Hg (about 286 mm H_2O) The difference between these, 11 mm Hg (about 150 mm H_2O) probably approximates the average pressure under which fluids escape from the capillaries into the perivascular or lymphatic spaces Since this is about the mean normal pressure in the subarachnoid space, it is clear (assuming capillary pressures to be similar throughout the body) that the normal outward flow of fluids from the tissues into the subarachnoid space must be under very low pressure and could be reversed by slight rises in subarachnoid pressure unless the arterial capillary pressure were simultaneously increased It must be assumed, however, that any reversal in flow would be rapidly antagonized by a compensatory increase in arterial capillary pressure as a vital defensive measure on the part of the body to protect the integrity of the supply of water, salts and other nutritive material to the nervous tissues, since a reversal of flow means essentially a cessation of the normal passage of water and its contained dialyzable substances from the blood into the tissue spaces Further, the increased subarachnoid pressure in acute inflammatory diseases of the central nervous system is doubtless due, in part at least, to an arterial hyperemia in the nervous tissues involving an increase in the passage of water and water-borne substances into the tissue spaces, and so into the subarachnoid space with which they are in direct communication Obviously, therefore, there is not only an increased resistance, in the presence of inflammatory disease, to a backward flow from the subarachnoid space into the perivascular spaces but the regurgitation, if artificially accomplished, would be even more rapidly offset than under normal conditions, and the substances (serum antibodies) so introduced, rapidly diluted, and expelled back into the subarachnoid space

The same compensatory mechanism must apply if the reversal of flow is accomplished by intravenous injection of hypertonic solutions, as has been proposed for therapeutic purposes by Aycock and Amoss (4) The body, in order to maintain the nutrition of the tissues, will rapidly dilute the blood, restore the osmotic pressure to normal and thus automatically check the abnormal drainage of tissue fluids back

into the blood and, simultaneously, the reversed flow in the perivascular spaces

That a temporary reversal of flow can be accomplished, either by raising the intrathecal pressure or by intravenous injection of hypertonic solutions, and that either of these methods may serve to introduce intrathecally injected substances into the perineuronal spaces for a brief period of time can hardly be doubted In poliomyelitis, however, the potential therapeutic value of such a route of administration is greatly lessened by the fact that so many of the perivascular spaces are obstructed by infiltrations of small cells, in just the areas which it is most desired to reach, and that a continuous, rather than a brief, supply of neutralizing antibodies in the spaces surrounding the nerve cells is requisite if the continuing descent of virus at such points is to be combatted

Under ordinary conditions of intrathecal injection it is highly probable that little of the serum reaches the nerve cells by the perivascular route, especially when precautions are observed *not* to increase the pressure, and that the only way by which it could reach them would be by absorption through the blood vessels into the general circulation, and thus indirectly by way of the blood stream On the other hand, when put directly into the blood stream the donated antibodies would have immediate, and *continuous* access to all parts of the tissues of the central nervous system, aided, no doubt, in reaching affected cells in infected areas by the accompanying increased vascular permeabilities incidental to the secondary inflammatory reaction As has been said in a preceding section, the outcome will then depend upon the relative concentrations of virus and antibody attained at a given point, and the maximum benefit therefore can only be obtained by *supplying the maximum concentration of antibodies in the blood at the earliest possible moment, and maintaining this concentration as long as is necessary*

The intramuscular route has the same disadvantages in the treatment of poliomyelitis as it has, for instance, in diphtheria, slow absorption, consequent low concentration of antibodies in the blood, delayed and submaximal effective action In poliomyelitis, even more than in diphtheria, the time element is of critical importance since the disease may progress within a few hours after its first recog-

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categorically if the work of Shaughnessy, Harmon and Gordon (94) had been repeated and confirmed on a large scale This is urgently needed, since their observations suggest that persons who actually develop the disease over the age of two years are relatively defective in their capacity to form immune substances as compared with others, and it appears from their studies and those of Aycock and Kramer, (5) that about eighty per cent of urban adults possess specific virucidal antibodies in the blood

Despite the defects in present-day serum therapy of poliomyelitis, certain beneficial effects may probably be traced to it As has already been remarked the outcome in a given case of poliomyelitic infection depends on the result of a series of local combats in the central nervous system, depending on the relative amounts of virus and antibody at each locus of infection, and essentially or mainly on the amount of virus at each Since the latter doubtless varies, we find that the advance of the infection is often halted at some points and not at others With an effective increase in circulating immune substances the extent of the halt may be increased and the extent of the advance diminished, thus, even with inadequate dosage of immune substances the advance may be less extensive but not completely prevented The observations of Aycock and his associates (7) confirm this assumption in a considerable degree, for while many of their treated patients showed residual paralysis, both the proportion of such cases and the extent of paralysis in them was significantly less than in the untreated It is therefore unnecessary, as proponents of the all-or-none criterion of therapeutic success might advocate, to discard these observations as meaningless or inconclusive They are on the contrary consonant with a partial benefit and in character with what might be expected from inadequate rather than worthless treatment While it is unlikely that fulminant or overwhelming infections will ever be controlled with certainty, there is reason to hope that improved methods of treatment will substantially further lessen the proportion of cases with paralysis and the extent of paralysis when it does occur

The potential usefulness of *foreign sera*, once regarded as negligible, now appears to be real and considerable While most individuals of foreign species do not produce specific antisera, various workers, among them Neustadter and Banzhaf (84), Fairbrother (25), Schultz

nition to a point where the motor cells are hopelessly involved Of all methods at present available for supplying immune substances to patients with acute poliomyelitis, *the intravenous administration of blood or serum, preferably repeated, from donors with known high concentrations of neutralizing antibodies in their serum and in the largest feasible amounts is the only one which gives any promise of effective therapy in cases of any severity and is the only method by which the effectiveness of serum therapy should be judged.*

The observance of such conditions is not impractical It requires the facilities of a laboratory equipped to make the necessary tests of donors for antipoliomyelitic antibodies, and it requires a sufficient number of immune donors to be made available in advance of the time when they are apt to be needed (the test requires about two weeks). A history of antecedent poliomyelitis in the donors is then entirely unnecessary, since the criterion of their usefulness is the ability of their serum to neutralize poliomyelitic virus It is desirable and possible by titration of serum, to obtain donors with high concentrations of immune substances in their serum One of ours has a titer of 1 60 and was recently used in a case of unusual severity In such cases, and whenever it is feasible, transfusion is preferred on the basis of safety and probable maximum effectiveness The intravenous use of stored serum, to which preservative is usually added, has certain obvious disadvantages, but if transfusion cannot be done, this method is preferable to the intramuscular for the reasons stated It is quite feasible to obtain larger stocks of pooled tested serum, if this method is preferred, than is possible with convalescent serum alone

The amounts of serum usually given are too small So long as one is restricted to the use of convalescent serum the supply—derived as it must be mainly from children—will be limited and inadequate Until more is known of the therapeutic effects in relation to viricidal units, the only safe rule is to give the largest amount compatible with safety For transfusions, here, the same rules in respect to amount should be used as for maximum transfusions in general

When serum of known antibody content is unavailable, it may even be, in my own opinion, preferable to use the pooled serum of healthy adults without a history of poliomyelitis to that of convalescents from the disease This statement would be made more positively and

categorically if the work of Shaughnessy, Harmon and Gordon (91) had been repeated and confirmed on a large scale. This is urgently needed, since their observations suggest that persons who actually develop the disease over the age of two years are relatively defective in their capacity to form immune substances as compared with others, and it appears from their studies and those of Aycock and Kramer, (5) that about eighty per cent of urban adults possess specific virucidal antibodies in the blood.

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and Gebhardt (93), and Weyer, Park and Banzhaf (103), have found with horses that exceptional individuals are capable of producing specific antibodies in effective concentration [15] Flexner and Lewis (45) noted a slight neutralizing power in sheep serum which could be enhanced by injections of virus, and more recently Howitt and her associates (55) have obtained promising results with both goats and sheep Immune monkey serum was used by Netter (83) many years ago but will probably never be available in important amounts

If foreign serum of high potency can be made available on a large scale, it might largely supplant human serum for general use, despite the increased risk of anaphylactic accidents and of severe serum sickness In view of the dangers of poliomyelitic infection, intravenous administration may be preferable with foreign serum, also

Summary The therapeutic value of antipoliomyelitic serum, human and foreign, remains to be determined, but should be subjected to test under optimal conditions before it is discountenanced Up to the present it cannot be said that such a test has been made The criteria of adequate serum treatment are the same as for other diseases serum of known high potency, sufficient amounts, administration at the earliest possible moment, administration by way of the blood stream to attain the maximum concentration of antibodies in the shortest possible time The respects in which treatment has frequently been faulty are, first, the use of serum of unknown, and probably often low, antibody content, the use of too small amounts, the administration by routes which fail to reach the blood stream promptly and effectively Convalescent serum, *per se*, has no advantage over "normal" serum, in either case, the value depends on the antibody content Intravenous injection of whole blood or serum in large amounts from donors tested for immunity appears to be the best method at present generally available Foreign serum of high antibody titer, when this can be supplied, may be still better

The results to be expected are not, for reasons given, complete prevention of paralysis in all cases, but rather a diminution of the extent of paralysis in treated, as compared with untreated cases,

[15] Schultz (personal communication) has recently immunized a horse to a point where 1 cc of its serum was capable of inactivating in vitro more than 50,000 minimal infective doses of virus

since it is inevitable that in many instances by the time diagnosis can be made, some of the motor cells have already been invaded and are inaccessible to therapy

X SUMMARY AND CONCLUSIONS

Poliomyelitis throughout its entire course is primarily and essentially an infectious disease of the central nervous system, caused by a strictly neurotropic virus Only when it is so regarded can its various clinical and pathological manifestations and the results of experimental investigation be harmoniously correlated and interpreted, and only then do the inherent contradictions and obscurities of previous conceptions of the disease begin to disappear The idea of a "systemic," extranervous phase preceding invasion of the central nervous system must be abandoned

The clinical course of the disease has been shown to correspond with the advance of infection through and within the central nervous system, and a consideration of the portal of entry (olfactory mucosa), of the distribution of the lesions, of the anatomy of the nerve tracts, of the character and chronological order of the symptoms leads to the conclusion that the infection follows a fairly well marked main route from the upper olfactory centers to the site in the anterior horns of the cord where it produces its most marked and disastrous effects This route leads through the olfactory nerves to the olfactory bulb, through the olfactory tracts to the interbrain (hypothalamus and thalamus), where it often excites early symptoms, through the spinothalamic tract to the posterior horns and intervertebral ganglia of the cord, where it produces the later preparalytic symptoms, and thence to the anterior spinal horns The main reason for believing that the infection descends along a sensory tract to the posterior horns rather than along motor tracts, such as those with relays in the midbrain, is the fact that in nearly all cases of poliomyelitis the sensory symptoms—predominantly pain, either spontaneous or on manipulation—precede the motor symptoms A second route leads from the hypothalamus to the medulla Since in the average case bulbar symptoms are absent or slight or transient, and since the main sensory tract leading from the medulla to the cord is apparently rarely affected, this route is regarded as being a subsidiary one

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In principle, the mode of propagation is by implantation and multiplication of virus in the ganglionic cell centers along the route with passage from one center to the next through the axons of the connecting nerve tracts, according to the hypothesis of Fairbrother and Hurst The tendency of the virus to die out in those centers where conditions for its survival are not optimal offers an explanation of the frequent occurrence of interruptions in the clinical progress of the disease (phenomenon of "halting"), the most striking instances of which are the "dromedary" phenomenon and the non-paralytic ("abortive") case

In accordance with the general conception of the disease as above outlined, its course may be divided into four successive stages or phases which are sometimes separated by intervals of symptomatic silence and sometimes occur in such rapid sequence that there is apparent overlapping The classification is shown in table 15

It is possible that the classification shown here may increase the facility of diagnosis by drawing more attention to the earliest manifestations of the disease, particularly the psychic, sensory and vegetative symptoms, and bringing their significance into better focus It is to be hoped that better cooperation of the neuropsychiatrist with the pediatrician and internist may be obtained in the future with the object of studying and defining the early symptomatology with greater precision

If, as is theoretically possible, the tendency to "halting" in the progress of the disease is due in some part to contact in the tissue spaces between circulating virucidal substances and virus passing from one neuron to the next, this would suggest the mode and technique of treatment which promise to be most effective The essential features of such treatment would be use of serum of known high neutralizing power, maximum safe dosage, intravenous administration to obtain the maximum concentration of antibodies in the blood stream at the earliest possible moment Treatment as at present generally practiced fulfils none of these requirements Intrathecal administration, without simultaneous use of intravenous hypertonic solutions is theoretically inadequate since serum so administered is unlikely to regurgitate at all or for more than a very brief time into the perivascular and perineuronal spaces against the normal

direction of flow of fluids in these channels which, in addition, are largely blocked by infiltrations of small cells On the other hand,

TABLE 15

Successive clinical phases of acute poliomyelitis

ROUTE OF INFECTION	ANATOMICAL SOURCE OF SYMPTOMS	CHARACTERISTIC SYMPTOMS
Phase I Cerebral, or diencephalic stage		
Olfactory bulb to hypothalamus and thalamus, (mid brain, medulla)	Hypothalamus, thalamus, medulla (?)	Fever, drowsiness alternating with restlessness and sleeplessness, vegetative disturbances (sweating, etc), *general* hyperesthesia, affective disturbances (apprehension, fear, anxiety, awareness of trouble, heightened affective sensibility, especially to pain), vomiting, headache
Phase II Stage of posterior poliomyelitis lower sensory stage		
Thalamus, through spinothalamic tract to posterior horns of cord, to posterior root ganglia	Posterior horns, posterior root ganglia	Localized pains and tenderness, disturbance of pain and temperature sensibility, pain on flexion of spine, pain to Kernig maneuver, increased tendon reflexes
Phase III Stage of anterior poliomyelitis lower motor stage		
Posterior horns and posterior root ganglia, through connector fibers to anterior horns, and columns of Clarke	Anterior horns, cells of columns of Clarke	A Twitchings tremor ataxia, weakness, diminution of reflexes B Flaccid paralysis, loss of reflexes
Phase IV Stage of recovery		
No further spread, infection dies out	Undestroyed cells gradually recover, inflammation subsides	Diminution of extent of paralysis, disappearance of pain and tenderness

serum administered intravenously would be favored in reaching the affected cells and tissues by the normal direction and conditions of flow from the capillaries and, in addition, by the conditions of in-

creased blood flow and vascular permeability resulting from t
flammatory reaction existing in the affected parts

Human serum for treatment may be selected either from pa
recovered from the disease or from "normal" persons not kno
have had it In either case, selection should be based on the
determination of the presence or absence, and preferably of th
centration, of immune substances in their blood Preliminary
ing is perfectly practicable, though expensive, and has, in fact, al
been put to use in practice It would be unfortunate, in my op
to permit the serum treatment of poliomyelitis to fall into disr
until some such attempt to improve the standards of the seru
its administration has been made and the results properly eval

Since the manuscript of this paper was completed (Sept
1932) a very considerable number of publications on poliom
and on the various related subjects discussed has appeared, refe
to which it has been impossible to include None of them has,
knowledge, invalidated the principal contentions herein offered.
experiments of Faber and Gebhardt, referred to on p 100, ha
just begun at that time but in revising the manuscript for the p
I have cited them because they offer direct confirmation of my
thesis of route-propagation otherwise based largely—perhap
heavily—on indirect evidence and clinical inferrence

I am deeply indebted to Dr E W Schultz, Professor of
teriology and to Dr J C Hinsey, Professor of Anatomy, bo
Stanford University, for their criticisms and many helpful sugges
and to Dr Stanley Cobb, Bullard Professor of Neuropatholo
Harvard University, for important critical comments, among
one which led to the inclusion of the reticular formation in the
tomical scheme The responsibility for the various inference
theories herein presented is, of course, entirely my own

BIBLIOGRAPHY

(1) Amoss, H L The cultivation and immunological reactions of the globoid
in poliomyelitis Jour Exp Med 25 545–555 (April) 1917

(2) Amoss, H L Virus diseases of man as exemplified by poliomyelitis In
Filterable Viruses Baltimore The Williams & Wilkins Co , 1928, 15

(3) Amoss, H L , and Taylor, E Neutralization of the virus of poliomyel
nasal washings Jour Exp Med 25 507–523 (April) 1917

(4) Aycock, W L, and Amoss, H L The treatment of acute poliomyelitis Preliminary note on use of hypertonic salt solution and convalescent human serum Jour Amer Med Assn 81 474 (Aug 11) 1923
(5) Aycock, W L, and Kramer, S D Immunity to poliomyelitis in normal individuals in urban and rural communities as indicated by the neutralization test Jour Prev Med 4 189–200 (May) 1930
(6) Aycock, W L, Luther, E H, and Kramer, S D Technic of convalescent serum therapy in poliomyelitis Jour Amer Med Assn 92 385 (Feb 2) 1929
(7) Aycock, W L, Luther, E H, McKhann, C F, Smith, E C, and Kramer, S D Preparalytic poliomyelitis treatment with convalescent serum Jour Infect Dis 45 175, 1929
(8) Bard, P The central representation of the sympathetic nervous system as indicated by certain physiological findings In The Vegetative Nervous System The Williams & Wilkins Co, Baltimore, 1930, 67–91
(9) Burnet, F M, and MacNamara, J Immunologic differences between strains of poliomyelitis virus Brit Jour Exp Path 12 57, 1931
(10) Burrows, M T Is poliomyelitis a disease of the lymphatic system? Arch Int Med 48 33 (July) 1931
(11) Cadwalader, W B Acute anterior poliomyelitis—a pathological study of three cases Univ Penn Contrib Neurology, 4 (not paged), 1908
(12) Clark, P F, and Amoss, H L Intraspinous infection in experimental poliomyelitis Jour Exp Med 19 217, 1914
(13) Clark, P F, Fraser, F R, and Amoss, H L The relation to the blood of the virus of epidemic poliomyelitis Jour Exp Med 19 223, 1914
(14) Clark, P F, Roberts, D J, and Preston, W S, Jr The passage of poliomyelitis virus through the intestinal tract Jour Prev Med 6 47 (Jan) 1932
(15) Clifton, C E, Schultz, E W, and Gebhardt, L P Ultrafiltration studies on the virus of poliomyelitis Jour Bact 22 7 (July) 1931
(16) Covell, W P Nuclear changes of nerve cells in acute poliomyelitis Proc Soc Exp Biol and Med 27 927 (June) 1930
(17) Dandy, W E, and Blackfan, K D Internal hydrocephalus An experimental and pathological study Amer Jour Dis Child 8 406–482, 1914
(18) Demole, V Pharmakologisch anatomische Untersuchungen zum Problem des Schlafes Arch f exp Path u Pharm 120 229, 1927
(19) Draper, G Acute poliomyelitis Philadelphia, P Blakiston's Son & Co, 1917
(20) Draper, G Significant problems in acute anterior poliomyelitis Jour Am Med Assoc 97 1139–1141 (Oct 17) 1931
(21) Dumpert, V Über die physiologische Bedeutung des Erbrechens Deutsch Ztschr f Nervenheilk 96 8, 1927
(22) Edinger, L Vorlesungen über den Bau der nervosen Zentralorgane des Menschen und der Tiere Bd I Das Zentralnervensystem des Menschen und der Saugetiere 8th edition F C W Vogel, Leipzig, 1911
(23) Faber, H K Transfusion donors as sources of immune serum for treatment of poliomyelitis Jour Amer Med Assn 96 935–937 (Mar 21) 1931
(24) Fahr, G, Kerkhof, A, and Conklin, C Normal osmotic pressure of the plasma proteins in man Proc Soc Biol and Med 28 718 (April) 1931

(25) FAIRBROTHER, R W Immunization of the horse with the virus of poliomyelitis and the production of an antiviral serum Brit Jour Exp Path 11 43 (Feb) 1930

(26) FAIRBROTHER, R W , AND HURST, E W The pathogenesis of, and propagation of the virus in, experimental poliomyelitis Jour Path and Bact 33 17–45, 1930

(27) FLEXNER, S The contribution of experimental to human poliomyelitis Jour Amer Med Assn 55 1105–1113 (Sept 24) 1910

(28) FLEXNER, S The Huxley lecture on some problems in infection and its control Lancet, 2 1271–1278 (Nov 9) 1912

(29) FLEXNER, S Recent advances in science in relation to practical medicine Some problems in infection and its control Science 36 685 (Nov 22) 1912

(30) FLEXNER, S Science, 73· 386 (Apr 10) 1931

(31) FLEXNER, S , AND AMOSS, H L Penetration of the virus of poliomyelitis from the blood into the cerebrospinal fluid Jour Exp Med 19 411, 1914

(32) FLEXNER, S , AND AMOSS, H L Localization of the virus and pathogenesis of epidemic poliomyelitis Jour Exp Med 20 249–268, 1914

(33) FLEXNER, S , AND AMOSS, H L The relation of the meninges and choroid plexus to poliomyelitis infection Jour Exp Med , 25 525, 1917

(34) FLEXNER, S , AND AMOSS, H L Persistence of the virus of poliomyelitis in the nasopharynx Jour Exp Med 29 379–395, 1919

(35) FLEXNER, S , AND AMOSS, H L Revived activity of the virus of poliomyelitis Jour Exp Med 39 191, 1924

(36) FLEXNER, S , AND CLARK, P F Epidemic poliomyelitis Eleventh note relation of the virus to the tonsils, blood and cerebrospinal fluid, races of the virus Jour Amer Med Assn 57 1685 (Nov 18) 1911

(37) FLEXNER, S , AND CLARK, P F A note on the mode of infection in epidemic poliomyelitis Proc Soc Exp Biol and Med 10 1, 1912–13

(38) FLEXNER, S , CLARK, P F , AND AMOSS, H L A contribution to the epidemiology of poliomyelitis Jour Exp Med 19 195–204, 1914

(39) FLEXNER, S , CLARK, P F , AND AMOSS, H L A contribution to the pathology of epidemic poliomyelitis Jour Exp Med 19 205–211, 1914

(40) FLEXNER, S , CLARK, P F , AND FRASER, F R Epidemic poliomyelitis Fourteenth note passive human carriage of the virus of poliomyelitis Jour Amer Assn 60 201 (Jan 18) 1913

(41) FLEXNER, S , AND LEWIS, P A The transmission of epidemic poliomyelitis to monkeys Jour Amer Med Assn 53 1913 (Dec 4) 1909

(42) FLEXNER, S , AND LEWIS, P A Epidemic poliomyelitis in monkeys The activity of the virus Jour Amer Med Assn 54 45–46 (Jan 1) 1910

(43) FLEXNER, S , AND LEWIS, P A Epidemic poliomyelitis in monkeys A mode of spontaneous infection Jour Amer Med Assn 54 535 (Feb 12) 1910

(44) FLEXNER, S , AND LEWIS, P A Experimental epidemic poliomyelitis in monkeys Sixth note, characteristic alterations of the cerebrospinal fluid and its early infectivity, infection from human mesenteric lymph node Jour Amer Med Assn 54 1140 (Apr 2) 1910

(45) FLEXNER, S , AND LEWIS, P A Experimental poliomyelitis in monkeys Eighth note further contributions to the subject of immunization and serum therapy Jour Amer Med Assn 55 662 (Aug 20) 1910

(46) Flexner, S , and Lewis, P A Experimental epidemic poliomyelitis in monkeys Jour Exp Med 12 227–255, 1910
(47) Flexner, S , and Noguchi, H Experiments on the cultivation of the microörganism causing epidemic poliomyelitis Jour Exp Med 18 461–485 (Oct) 1913
(48) Forssner, G , and Sjövall, E Ueber die Poliomyelitis acuta samt einen Beitrag zur Neuronophagienfrage Ztschr f klin Med 63 1, 1907
(49) Francis, T D , and Moncreiff, W T Second attack of poliomyelitis, after an interval of fifteen years Jour Nerv and Ment Dis 49 273–281 (April) 1919
(50) Harbitz, T , und Scheel, O Pathologisch anatomische Untersuchungen über akute Poliomyelitis und verwandte Krankheiten von den Epidemien in Norwegen 1903–1906 Videnskahs-Selskahets Skrifter, I Math naturv Klasse 1907 No 5 Christiania In Kommission bei Jacob Dyhwad 1907
(51) Hatcher, R A , and Weiss, S Studies on vomiting Jour Pharmacol 22 139, 1923
(52) Herrick, C J Brains of rats and men A survey of the origin and biological significance of the cerebral cortex Univ Chicago Press, Chicago, 1926
(53) Hewlett, A W Pathological physiology of internal disease Functional pathology D Appleton and Co , New York and London, 1923, 499–500
(54) Hilding, A Ciliary activity and course of secretion currents of the nose Proc Staff Meetings Mayo Clinic 6 285 (May 13) 1931
(55) Howitt, B T , Shaw, E B , Thelander, H , and Limper, M The immunization of goats and sheep to poliomyelitis virus clinical application of their serums Jour Amer Med Assn 96 1280 (Apr 18) 1931
(56) Huber, G C , and Crosby, E C Somatic and visceral connections of the diencephalon In The Vegetative Nervous System The Williams & Wilkins Co , Baltimore, 1930, 199–248
(57) Hurst, E W The histology of experimental poliomyelitis Jour Path and Bact 32 457, 1929
(58) Hurst, E W A further contribution to the pathogenesis of experimental poliomyelitis inoculation into the sciatic nerve Jour Path and Bact 33 1133–1143, 1930
(59) Hurst, E W The occurrence of intranuclear inclusions in the nerve cells in poliomyelitis Jour Path and Bact 34 331, 1931
(60) Jungeblut, C W , and Spring, W J A note on the propagation of the virus in experimental poliomyelitis Proc Soc Exp Biol and Med 27 1076 (June) 1930
(61) Kadyi, H Über die Blutgefasse des menschliches Rückenmarkes Gubryno wicz & Schmidt, Lemberg, 1889
(62) Keller, A D , and Hare, W K The hypothalamus and heat regulation Proc Soc Exp Biol and Med 29 1069 (June) 1932
(63) Kellogg, W H The present status of convalescent serum therapy Jour Amer Med Assn 93 1927–1931 (Dec 21) 1929
(64) Key and Retzius Anatomie des Nervensystems und des Bindesgewebe Stockholm, 1876 Cited by Weed (6)
(65) Kling, C , and Pettersson, A Keimträger bei Kinderlahmung Deutsch med Wchnschr 40 320 (Feb 12) 1914

(66) KLING, C , WERNSTEDT, W , AND PETTERSSON, A Recherches sur le mode de propagation de la paralysie infantile epidémique (maladie de Heine-Medin) Ztschr f Immunitatforsch Orig 16 17, 1912

(67) LA FETRA, L E , AND SCHWARZ, A B Epidemic poliomyelitis Report on the New York epidemic of 1907 by the Collective Investigation Committee Dr B Sachs, Chairman Jour Nerv and Ment Dis Pub Co , New York, 1910 Section II, 29–37

(68) LANDIS, E M Micro-injection studies of capillary blood pressure in human skin Heart 15 209, 1930

(69) LANDSTEINER, K , AND LEVADITI, C La transmission de la paralysie infantile aux singes Compt rend Soc d biol 67 592 (Nov 27) 1909

(70) LANDSTEINER, K , AND LEVADITI, C Étude expérimentale de la poliomyelite aigue (maladie de Heine-Medin) Ann de l'Inst Pasteur 24 833 (Nov) 1910

(71) LANDSTEINER, K , LEVADITI, C , AND DANULESCO, V Présence du virus de la poliomyélite dans l'amygdale des singes paralysés et son élimination par le mucus nasal Compt rend soc biol 71 558, 1911

(72) LANDSTEINER, K , LEVADITI, C , AND PASTIA, C Recherches du virus dans les organes d'un enfant atteint de poliomyélite aigue Compt rend acad scienc 152 1701 (June 12) 1911

(73) LEINER, C , UND VON WIESNER, R Experimentelle Untersuchungen uber Poliomyelitis acuta Wien med Wchnschr 60 2482 (Oct 15) 1910

(74) LEINER, C , AND VON WIESNER, R Experimentelle Untersuchungen uber Poliomyelitis acuta anterior Wien klin Wchnschr 23· 91, 1910

(75) LEVADITI, C , AND DANULESCO, V Conditions qui président à la transmission de la poliomyélite Compt rend soc biol 72 606, 1912

(76) L'HERMITTE, J , AND TOURNAY, A Rapport sur le sommeil normal et pathologique Rev neurol 1· 751–887, 1927

(77) LOVETT, R W , AND LUCAS, W P Infantile paralysis A study of 635 cases, with special reference to treatment Jour Am Med Assn 51 1677 (Nov 14) 1908

(78) LUCAS, W P , AND OSGOOD, R B Transmission experiments with the virus of poliomyelitis Finding the virus in the nasal secretion of a human carrier four months after the acute stage of a second attack of poliomyelitis Jour Amer Med Assn 60 1611 (May 24) 1913

(79) MEDIN, O L'état aigu de la paralysie infantile (mémoires originaux) Arch d méd d enfants 1 257, 1898

(80) A monograph on the epidemic of poliomyelitis (infantile paralysis) in New York City in 1916, based on the official reports of the bureaus of the Department of Health Published under the direction of the Department of Health of New York City 1917

(81) MOTT, F W The Oliver-Sharpey lectures on the cerebrospinal fluid Lancet, 2 1, 1910

(82) MULLER, EDUARD Die spinale Kinderlahmung Eine klinische und epidemiologische Studie J Springer, Berlin, 1910

(83) NETTER, A Guérison rapide à la suite d'injections de sérum de singe immunisé d'une poliomyélite à la phase préparalytique Résultat antérieure identique après injection de sérum d'anciens malades Méningites dues au virus de la poliomyélite chez de jeunes enfants Bull et Mém Soc Méd d Hop de Paris, 46 537 (Apr 7) 1913

(84) Neustaetter, M , and Banzhaf, E J An antipoliomyelitis horse serum Preliminary report Jour Amer Med Assn 68 1531 (May 26) 1917
(85) Parker, G H Smell, taste and allied senses in the vertebrates Monographs on experimental biology J B Lippincott Co , Philadelphia and London, 1922
(86) Peabody, F W , Draper, G , and Dochez, A R A clinical study of acute poliomyelitis Monographs of the Rockefeller Institute for Medical Research, No 4 (June 24), 1912, New York
(87) Ransom, F A modern view of tetanus Lancet 2 928 (Dec 22) 1917
(88) Redlich, E Beitrag zur pathologischen Anatomie der Poliomyelitis anterior acuta infantum Wien klin Wchnschr 7 287 (Apr 19) 1894
(89) Rhoads, C P Immunity following the injection of monkeys with mixtures of poliomyelitis virus and convalescent human serum Jour Exp Med 53 115, 1931
(90) Rissler, J Zur Kenntniss der Veränderungen des Nervensystems bei Poliomyelitis anterior acuta Nord med Arkiv 20 1–63, 1888
(91) Romer, Paul H Epidemic infantile paralysis (Heine Medin disease) Transl by H R Prentice John Bale, Sons and Danielsson, Ltd , London, 1913
(92) Schultz, E W Recent advances in the study of poliomyelitis Jour Pediat 1 358 (Sept) 1932
(93) Schultz, E W , and Gebhardt, L P Antipoliomyelitis serum production in the horse Proc Soc Exp Biol and Med 28 412 (Jan) 1931
(94) Shaughnessy, H S , Harmon, P H , and Gordon, F B Neutralizaton of the virus of poliomyelitis by human sera Proc Soc Exp Biol and Med 27 742 (May) 1930
(95) Shaw, E B , Thelander, H E , and Fleischner, E C Convalescent serum in preparalytic cases of poliomyelitis, results of intramuscular administration Jour Amer Med Assn 85 1555 (Nov 14) 1925
(96) Still, G F Second attacks of acute poliomyelitis and the minimum duration of immunity Arch Dis Childhood 5 295 (Oct) 1930
(97) Taylor, E , and Amoss, H L Carriage of the virus of poliomyelitis, with subsequent development of the infection Jour Exp Med 26 745, 1917
(98) Thomsen, O Experimentelle Untersuchungen über Poliomyelitis Berlin klin Wchnschr 49 63, 1912
(99) Tilney, F , and Riley, H A The form and functions of the central nervous system Second edition Paul B Hoeber, Inc , New York, 1928
(100) Wallenberg, A Das basale Riechbündel des Kaninchens Anat Anzeig 20 175, 1902
(101) Ween, L H The absorption of cerebrospinal fluid into the venous system Amer Jour Anat 31 191, 1922
(102) Ween, L H The cerebrospinal fluid Physiological Reviews 2 171–203 (April) 1922 This paper reviews Weed's earlier work dating from 1914 and later
(103) Weyer, E R , Park, W H , and Banzhaf, J A potent antipoliomyelitic horse serum concentrate and its experimental use in infected monkeys Jour Exp Med 53 553, 1931
(104) Wickman, I Die akute Poliomyelitis bzw Heine Medinsche Krankheit M Lewandowsky, Handbuch der Neurologie, Bd 2, Spezielle Neurologie I , 807–910 Berlin, J Springer, 1911

(105) COBB, S The cerebrospinal blood vessels In Cytology and cellular pathology of the nervous system Edit Wilder Penfield Vol 2 Paul B Hoeber, Inc New York, 1932

(106) CUSHING, H Papers relating to the pituitary body, hypothalamus and parasympathetic system C C Thomas Springfield, Ill and Baltimore, Md , 1932

(107) FLEXNER, S , AND AMOSS, H L Experiments on the nasal route of infection in poliomyelitis Jour Exp Med 31 123, 1920

(108) HOPKINS, A E The olfactory receptors in vertebrates Jour Comp Neurol 41: 253–289, 1926

(109) PAPEZ, J W. Reticulo-spinal tracts in the cat Marchi method Jour Comp Neurol 41: 365–399, 1926

(110) SPIEGEL, E A The centers of the vegetative nervous system Bull Johns Hopkins Hosp 50 237–252, 1932

IDIOPATHIC HYPOCHROMIC ANEMIA

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CONTENTS

INTRODUCTION

With a momentum that suggests a new discovery, there has appeared in the past three years a series of reports concerning a hypochromic, microcytic type of anemia which occurs most commonly in women thirty to fifty years of age, and is associated in at least the great majority with defective gastric secretion It is strange indeed that, ever since Fenwick (27), in 1870, expressed the opinion that atrophy of the stomach was the primary disorder in his patient, so much attention should have been devoted to the hypothesis that some disturbance in the gastro-intestinal tract is related to the development of pernicious anemia, and yet so little interest was aroused by cases of hypochromic anemia associated with achlorhydria Examination of the few reports which appeared until 1929 (24, 25, 9, 85, 26) suggests that such cases had simply been overlooked by the majority of physicians rather than that a new disorder has appeared Physicians were satisfied to rule out pernicious anemia and their curiosity ended when the disorder was labelled "secondary anemia" The vagueness of many of the complaints, the multiplicity of the symptoms, the listlessness of the patients are all features which "would hardly incite clinical enthusiasm" (20) It is not unlikely that the recent discoveries in pernicious anemia have aroused so much interest in the study of the blood and its relation to gastric secretion that, as a consequence, attention has finally been drawn to a clinical entity which has always existed

Although Einhorn (22) in 1903 recorded three instances in which anemia with low color index was associated with achylia, he did not call attention to these cases and it seems that Faber (24, 25) was the first to recognize as a nosological entity cases of "simple anemia" associated with achylia His first paper in 1909 was amplified four years later by another in which was considered the frequency of various types of anemia among 207 instances of idiopathic achylia, that is, achylia not associated with carcinoma, tuberculosis or other diseases He noted anemia (hemoglobin less than 80 per cent) in 59 cases or 28 5 per cent Among these there were 15 instances of pernicious anemia while in 37 cases the color index was below one The anemia was particularly severe in 22 of the latter Faber pointed out that 19 of these 22 patients were women, their symptoms were vague and the anemia was very chronic No cause for the anemia could be found and Faber raised the question whether the anemia might not be related to the achylia This question he himself answered in the affirmative It is of special interest, in view of opinions expressed more recently, that Faber distinguished these cases from chlorosis In a later paper (1924) he called attention to the effectiveness of large doses of iron in treatment and recognized the tendency of the anemia to relapse

Since Faber's first publication, this "simple" anemia has been mentioned incidentally in studies of the blood of patients with achlorhydria of undetermined origin (85, 37, 68, 12), and in several other papers (73, 9, 86), however, with certain exceptions which will be discussed later, no papers dealing with this idiopathic hypochromic anemia as a clinical entity appeared until 1929 In the past few years, many reports have been published so that data are now available concerning 498 cases (93a, 84, 53, 1, 20, 32, 57, 55, 18, 29, 11, 25, 73a, 79, 59, 92) Descriptions have been presented under a variety of names Cases have been reported in which achlorhydria has not been present Instances of hypochromic anemia associated with dysphagia and other cases of such anemia occurring during pregnancy have been recorded The pathogenesis of the anemia has been discussed and its right to recognition as a disease entity has been disputed It seems timely, therefore, to attempt to sketch the clinical picture as afforded by the cases reported, and to discuss the questions which have arisen The discussion is supplemented by our own observations in 25 cases

TABLE 1

Summary of findings in 25 cases of idiopathic hypochromic anemia

SEX

23 female
2 male

AGE

22–74 years
Average 43 years
64 per cent 35–50 years
16 per cent under 35 years
20 per cent over 50 years

RACE

22 white
3 colored
(2 mulatto)

ENTRANCE COMPLAINTS

Of *anemia*, in 84 per cent (21 cases) (weakness 12 cases, dyspnea 4, anemia 2, palpitation 1, choking 1)
Gastro-intestinal, in 56 per cent (14 cases) (pain 7 cases, vague digestive complaints 5, sore mouth 1, sore tongue 1, difficulty in swallowing 1)
Nervous, in 32 per cent (8 cases) (nervousness 3 cases, headache 2, vague pain 2, paraesthesias 1)
Menstrual, in 12 per cent (3 cases) (irregularity 1, pain 1, menorrhagia 1)

SYMPTOMS

Of *anemia*, 84 per cent (21 cases)
Gastro-intestinal, 56 per cent (14 cases)
Paraesthesias, 36 per cent (9 cases)
Menstrual, 32 per cent (8 cases) (menorrhagia 4 cases, amenorrhoea 2, irregularity 2)
Sore tongue or mouth, 32 per cent (8 cases)
Hemorrhoids, 20 per cent (5 cases)

PHYSICAL FINDINGS

Color—Whitish pallor, 72 per cent (18 cases)
Yellowish pallor, 12 per cent (3 cases)
Brownish pallor, 16 per cent (4 cases)
Constitution (body build)—Asthenic 24 per cent
Hyposthenic 33 per cent
Sthenic 33 per cent
Hypersthenic 10 per cent
Nutrition—Thin 32 per cent
Normal 36 per cent
Obese 32 per cent

TABLE 1—*Concluded*

PHYSICAL FINDINGS—*Concluded*

Color of eyes—Blue or grey, 75 per cent of white patients
Hair prematurely grey, 20 per cent
Tongue, papillary atrophy, 64 per cent (includes atrophy limited to edges of tongue)
Spleen, palpable, 50 per cent, *liver* palpable, 18 per cent
Koilonychia, or marked longitudinal ridging with brittleness of nails, 40 per cent
Neurological signs, none

ETIOLOGY

Duration of symptoms, 2 to 22 years, average 8 years
Symptoms commenced in early adult life, 24 per cent
Surgical operations performed at commencement of, or in attempt to relieve symptoms, 20 per cent
Symptoms dated from onset of infections or other debilitating disease, 24 per cent
Symptoms definitely related to pregnancies, 20 per cent
Diet poor, 32 per cent

GASTRIC ANALYSIS

Achlorhydria by Ewald meal, 83 per cent (20 of 24 cases)
Achlorhydria by histamine test, 60 per cent (12 of 20 cases)
Achlorhydria to histamine test—12 cases
Achlorhydria to Ewald test (histamine not used)—4 cases
Achlorhydria to Ewald test but acid after histamine—4 cases
Hypochlorhydria—2 cases
Normal hydrochloric acid—2 cases

BLOOD Findings when patient was first seen

R B C Average 4 15 million (1 50 to 5 86 million) 90 per cent between 3 00 and 5 15 million
Hemoglobin Average 7 7 grams per 100 cc blood (2 6 to 11 6 grams) 74 per cent between 6 0 and 10 0 grams
Volume packed R.B C Average 29 5 cc per 100 cc blood (16 8 to 38 0 cc) 80 per cent between 23 and 35 cc
Mean corpusculor volume, average 65 c μ (50 to 83 c μ) 75 per cent between 55 and 74 c μ
Mean corpuscular hemoglobin, average 18 $\gamma\gamma$ (11 to 24 $\gamma\gamma$) 70 per cent between 15 and 21 $\gamma\gamma$
Mean corpusculor hemoglobin concentration, average 27 per cent (22 to 31 per cent) 83 per cent between 25 and 30 per cent
Morphology of red cells—Elliptical red cells noted in all cases
Leucocytes—Average 5,500 (4,000 to 7,000) per c.mm
Platelets—200,000 to 250,000 per c mm (Rees and Ecker method)

ETIOLOGIC FEATURES

Sex The almost exclusive occurrence of idiopathic hypochromic anemia in women (96 per cent) is an extraordinary feature of this disorder Only 18 cases have been heretofore recorded in men (89, 1, 20, 32, 55, 17, 18, 25) In five of these patients the anemia developed some years after a gastric operation

We have had two male patients One of these, a man of 40 years, (L B , table 2) is of special interest because his symptoms—weakness, indigestion, moderate shortness of breath and tightness in the chest on exertion, sore tongue and tingling in the hands and feet—suggested pernicious anemia and he was referred to us because "his blood did not fit " The anemia was microcytic and hypochromic in type He looked pale and exhausted The tongue was smooth about the edges There were no abnormal neurologic findings Gastric analysis revealed free hydrochloric acid of 12 Other examinations were negative and no cause for the anemia could be discovered Treatment with large doses of iron has been successful in relieving all his symptoms and he is now able to work for the first time in two years Dameshek has described a similar case (17)

Age In figure 1, the age distribution of 260 cases (55, 25, 60a, 93a, 17, 53, 73a, 32) is indicated Sixty per cent of the cases were encountered between the ages of 30 and 50, and 82 per cent between 20 and 50 years The most striking feature is the marked decrease in the incidence of this type of anemia after 50 years of age It should be pointed out that these statistics represent the age at discovery and not the age at onset of the anemia It is indeed quite unusual for this anemia to commence in women after the menopause Nevertheless, it does not seem to be true, as some writers (84) have suggested, that idiopathic hypochromic anemia is never encountered after reproductive functions have ceased

Race We have found no reports of cases of idiopathic hypochromic anemia among negroes but it should be pointed out that all of the publications, with one exception, have come from localities where few members of this race are found Our own data, however, suggest that this anemia is not common among negroes for we have encountered only three cases and two of these patients were mulattoes It is well to

recall, nevertheless, that anemia is less likely to be discovered in this race and that the clinical picture more often may be obscured by associated infections It is thus difficult to make a proper estimate of the occurrence of idiopathic hypochromic anemia in the negro race Keefer (44a) states that this type of anemia is not infrequent among Chinese patients

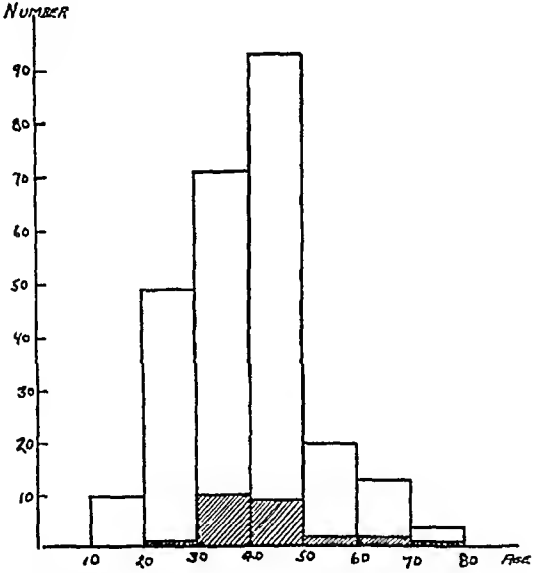

FIG 1 AGE INCIDENCE OF IDIOPATHIC HYPOCHROMIC ANEMIA

Two hundred and sixty reported cases The shaded portion represents our own twenty five cases

Constitutional type Witts (89) and Waugh (84) state that the majority of these patients are slender and asthenic This has not been the case with our patients, most of whom were hyposthenic or sthenic in build Like Witts, however, we have been impressed by the resemblance of some patients to the type so frequently encountered in

pernicious anemia with light-colored eyes set widely apart, prematurely gray hair and wide costal angles (table 1)

Familial incidence As in pernicious anemia, it is not unusual to find a family history of anemia in patients suffering from idiopathic hypochromic anemia In several instances pernicious anemia has been

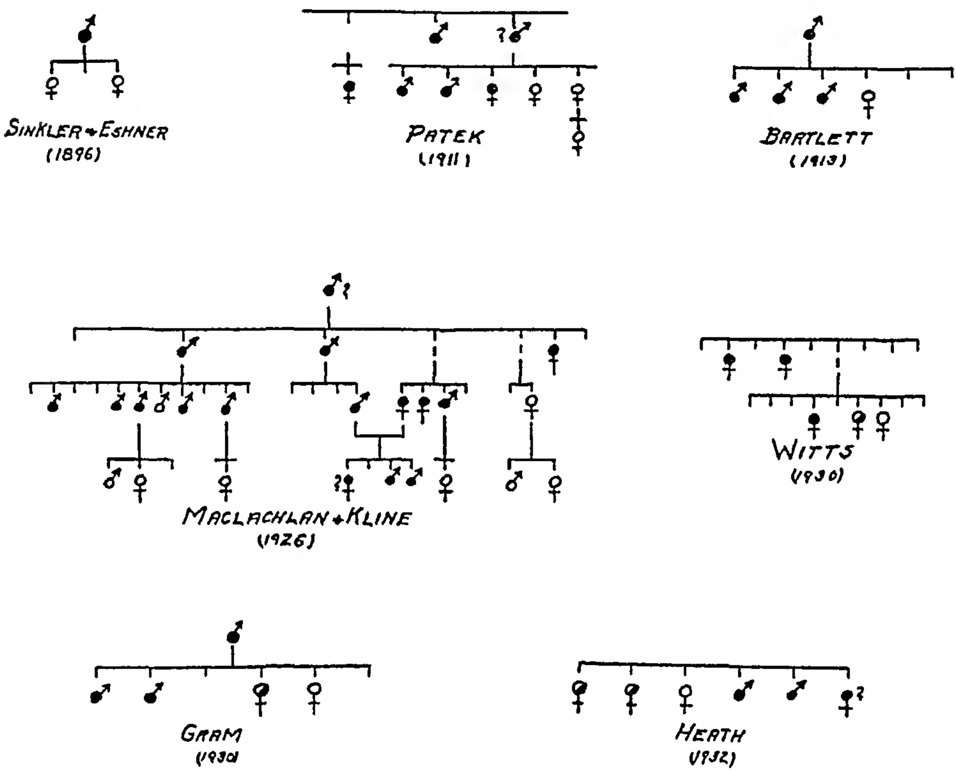

FIG 2 SEVEN FAMILIES IN WHICH BOTH PERNICIOUS ANEMIA AND HYPOCHROMIC ANEMIA WERE ENCOUNTERED

Black circles, pernicious anemia, open circles, hypochromic anemia, circles half open, half black, cases in which hypochromic anemia subsequently changed to pernicious anemia For the sake of simplicity members of these families who had no anemia are indicated only by short strokes and their sex is not given

noted in the male membe[illegible] ly whereas [illegible] suffered from a "seconda[illegible] Such cases [illegible]rted by Sinkler and Eshner ([illegible] Mac[illegible] [illegible]1), Hurst (40), Gram (30), [illegible] (35), [illegible]) (fig 2) The diagnosis of [illegible] in the [illegible]

these cases was probably quite correct Whether the hypochromic anemia encountered was in each case the same as idiopathic hypochromic anemia is more difficult to determine The information in most of the early reports is scanty, there being little more than the statement that no cause for the anemia could be discovered It is noteworthy that one of the members of the family of Maclachlan and Kline was considered, on the basis of clinical symptoms, to be suffering from pernicious anemia but the color index was 0 5 It seems not unlikely that this man had idiopathic hypochromic anemia and we have so designated him in figure 2 Another member of this family had marked hypochromic anemia and hypochlorhydria However, in the remaining six instances of hypochromic anemia in this family the secretion of hydrochloric acid was normal. The cases of hypochromic anemia in the families described by Gram, Witts, and Heath were probably true cases of idiopathic hypochromic anemia The patients described by these authors are of special interest because in several instances the microcytic hypochromic anemia later changed to the macrocytic type (pernicious anemia)

The families cited above are of course isolated instances and have been reported because of their extraordinary nature It is difficult to determine how frequently less striking family histories may be encountered Although special enquiry for familial cases was not made in his cases, a family history of anemia was given by three of Witts' 50 patients (89) A family history of anemia was discovered in two of 22 of our own cases in which enquiry was made The father of one of our patients had died of pernicious anemia In discussing her father's illness this patient remarked that she resembled her father in nervous disposition and in build, coloring and features The brother of another patient's father and the sister of her mother, had married and their daughter had been a patient in this hospital at the age of eighteen years She had had chlorosis and interestingly enough her blood findings were almost identical with those of our own patient Unfortunately no gastric analysis had been made

Hygienic factors Although patients have been found in all classes of society, there can be little doubt that poor hygienic surroundings contribute to the continuation and aggravation of the anemia We have been impressed with the frequency of a story of inadequate con-

valescence in the cases which commenced during pregnancy In a number of instances, moreover, the diet has been poor, although examination of case histories does not suggest that defective diet is responsible for the development of anemia in at least the majority of cases Nevertheless, it is true that in not a few cases flatulence, dyspepsia and poor appetite have led to the taking of a poorly balanced, inadequate diet rich in carbohydrates and poor in hemoglobin-building foods, with the result that a vicious circle of anemia, poor diet and more severe anemia may have become established

SYMPTOMATOLOGY

Onset The onset of idiopathic hypochromic anemia is characteristically insidious The time at which the patient calls for the physician's help is of course influenced by many factors not concerned with the anemia itself, but it is unusual for the patient to present herself before the hemoglobin falls to 10 grams (70 per cent) and it is often much lower than this The typical story is one of long continued ill-health In our cases the duration of symptoms varied from 2 to 22 years and averaged 8 years In Witts' series (89) the average duration of symptoms was 5 years In as many as 25 per cent of our cases complaints had been present since early adult life In an equal number symptoms were dated from the time of onset of some infection or other debilitating disease, the patients stating that they had never regained full strength and vigor since that time In several cases, some operation preceded the development of complaints In 17 per cent of our patients the onset of symptoms was definitely associated with pregnancy

Entrance complaints Complaints are characteristically vague and indefinite and they may call to mind a great variety of diseases All writers, however, stress the frequency with which weakness and ready fatigue, and an ever present feeling of "dead-tiredness" are the major

complaints, the anemia being discovered accidentally Thus one of our patients was referred because of the pallor of her retinae observed by an ophthalmologist whom she had consulted on account of a film over her eyes (uveitis) Although her hemoglobin was only 8 5 grams (59 per cent) she insisted that she was perfectly well She admitted having been told that she was anemic six years before but she was not concerned about this It seems rather characteristic of these patients that they become adjusted to a state of chronic ill health

Gastro intestinal system Vague complaints referred to the gastrointestinal tract are quite common in this disorder and include such symptoms as abdominal pain or distress, loss of appetite, flatulence, eructation, nausea, constipation, and sometimes vomiting or diarrhoea The latter occurred in eleven of Witts' 50 cases (89), but in Meulengracht's (55), Haden's (32), and in our series this was not a prominent symptom Occasionally diarrhoea, resulting from the achlorhydria, may become a major complaint As the consequence of these gastrointestinal symptoms, many of these patients become extraordinarily careful about their choice of food and, finding that carbohydrates cause least distress, they partake of a diet which is least efficient in blood regeneration

Sore tongue or sore mouth are frequently encountered Symptoms referred to the tongue or mouth were noted in approximately 28 per cent of 238 cases As Meulengracht (55) and others (44, 57) have stated, however, the glossitis rarely approaches the frequency and intensity observed in pernicious anemia Thus in only one of our cases was the sore tongue a sufficiently prominent symptom for it to be mentioned by the patient without questioning

Occasionally the *stomatitis* is very severe One of our patients had suffered from intermittent attacks of sore mouth for 12 years She described it to be "like thrush in a baby " During the attacks the corners of her mouth became sore and cracked, and on the mucous membrane of the cheeks small, pale blister-like lesions surrounded by a slight area of erythema appeared The tongue at the same time became dull red With relief of the anemia these symptoms disappeared but several months after treatment was discontinued, the sore mouth and anemia returned

Dysphagia In the past few years there has been described a clinical

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SYMPTOMATOLOGY

Onset The onset of idiopathic hypochromic anemia is characteristically insidious The time at which the patient calls for the physician's help is of course influenced by many factors not concerned with the anemia itself, but it is unusual for the patient to present herself before the hemoglobin falls to 10 grams (70 per cent) and it is often much lower than this The typical story is one of long continued ill-health In our cases the duration of symptoms varied from 2 to 22 years and averaged 8 years In Witts' series (89) the average duration of symptoms was 5 years In as many as 25 per cent of our cases complaints had been present since early adult life In an equal number symptoms were dated from the time of onset of some infection or other debilitating disease, the patients stating that they had never regained full strength and vigor since that time In several cases, some operation preceded the development of complaints In 17 per cent of our patients the onset of symptoms was definitely associated with pregnancy

Entrance complaints Complaints are characteristically vague and indefinite and they may call to mind a great variety of diseases All writers, however, stress the frequency with which weakness and ready fatigue, and an ever present feeling of "dead-tiredness" are the major complaints Symptoms which are usually associated with anemia, such as weakness, shortness of breath, palpitation and choking sensations were the entrance complaints of 84 per cent of our cases Only superseded by these, however, were the symptoms referred to the gastro-intestinal tract (56 per cent) while nervous and menstrual symptoms were somewhat less common (table 1) A few patients have no

Auerbach's plexus Kelly suggested that the sensory portion of tl nervous arc might have become hyperesthetic as the result of irritatic by foreign bodies, fissures or inflammation with consequent hype activity of the motor fibres and the subsequent development of a "nerv habit"

Paterson called attention to the common association of this spa modic dysphagia with superficial glossitis He remarked, as did Kell that these patients often were forced to take a semi-solid diet on a count of their dysphagia He described his patients as pale and sallo and a number had lost weight Their tongues were excessively smoo and glossy Whitish patches were noted on the dorsum of the tongi and on the buccal mucous membranes, and the angles of the mou were frequently cracked The mucosa of the pharynx looked ve thin and appeared to have lost its suppleness and resiliency

In 1922 Vinson (81) reported 69 cases collected from the Mayo Clin records He stated that Plummer had first noted this condition 1914 Fifty-seven of Vinson's patients were women He was ir pressed by the frequency with which the symptoms had started abrupt at a time when the patient choked over a piece of solid food In patients the hemoglobin was below 60 per cent In twelve the sple was palpated Oesophagoscopy revealed no abnormality and passa of a bougie, together with treatment of the anemia with iron, was fc lowed by relief of symptoms

In a subsequent review of the Mayo clinic cases, Moersch and Co ner (59) collected 65 cases for which adequate data were availabl These data further emphasized the great preponderance of this dy phagia in women, and the frequent association of anemia of a hyp chromic type with palpable spleen and glossitis or stomatitis In 8 10 patients examined, achlorhydria was found Paresthesias we noted in five patients, and diarrhoea in an equal number

Subsequent reports (38, 66, 13, 42, 92, 29) have served to emphasi the features already mentioned It is clear that glossitis, stomatit and anemia are commonly associated with this type of dysphagi Achlorhydria was noted in 11 of Witts' 13 patients (92) and in all s of those studied by Graham and Johnson (29)

Opinions concerning the cause of the dysphagia are varied The e planation proposed by Kelly has already been mentioned Hurst (3

suggested that spasm results from inflammatory changes in the nerve endings which are produced by the streptococcus longus In view of the usual anamnesis of these patients, Cameron (13) has suggested that in these cases a vicious circle operates Debility and anemia associated with the climacteric, changes in the pharyngeal mucosa, dysphagia, limitation of food, accentuation of anemia and aggravation of all the symptoms, is a frequently noted series of events He does not consider the anemia to be due to dietary deficiency and he states that the anemia is not due to dysphagia He has observed a case in which anemia of the same type reappeared without dysphagia after iron therapy had been discontinued

The occurrence of this syndrome almost exclusively in women 30 to 50 years of age, the presence of glossitis and stomatitis, achlorhydria, splenomegaly, koilonychia, paresthesias without objective neurologic findings, as well as a microcytic, hypochromic anemia which responds in a spectacular fashion to the administration of large doses of iron, make up a clinical picture indistinguishable from idiopathic hypochromic anemia and differentiated only by the presence of dysphagia. Although in many instances all other symptoms have been reported as

Davies (21) refers to the occurrence of *hematemesis* without apparent cause in 3 of his patients In view of the resemblance of this triad of anemia, splenomegaly and hematemesis to Banti's syndrome, the occurrence of this symptom is of special interest We have encountered one such case

Hematemesis, melena, negative gastro-intestinal tract except for achlorhydria, microcytic hypochromic anemia, paraesthesias, koilonychia R A, a white American housewife 45 years of age, first appeared at this hospital in October 1931 complaining of pain over the sacrum, tip of the spine and occipital region of the head, as well as a feeling of pressure and soreness in various parts of the body Her sister had died of tuberculosis at 22 years of age, and her father, two brothers and another sister were known to be suffering from this disease The patient, however, seemed to be free of this infection and until 1924 had been in excellent health She had been pregnant six times and had miscarried once In 1924 weakness and tiredness appeared, without apparent cause Three years later, the menstrual periods which had been perfectly regular, became irregular and the flow became very copious The latter symptoms were alleviated by a hysterectomy in 1929 In spite of this, however, tiredness and weakness continued

In December 1930, she suddenly became weak and dizzy and this was followed by the passage of large quantities of black blood per rectum There was no pain Four days later she had a sudden attack of vomiting and brought up a moderate quantity of dark blood

These symptoms disappeared completely and the patient gradually regained some strength In December 1931, the melena and hematemesis reappeared in the same manner as in the first attack and disappeared as quickly After three months confinement to bed the patient regained some strength but even when she was first seen at this hospital in June 1932, she was weak and stated that she tired very readily There were few additional symptoms There was no cough The appetite was moderate and there were no gastro-intestinal symptoms The diet was apparently normal Her weight had increased from 100 to 133 pounds since December Her tongue had never been sore Occasionally she felt numbness and tingling in the legs On questioning she stated that in the past six months her nails had been sore and broke very readily

Examination revealed a quiet, very pale, exhausted looking woman She was of the sthenic habitus and had blue eyes The body tended to be somewhat obese The mucous membranes and skin showed no evidence of telangiectases The tongue was smooth and shiny with definite papillary

atrophy The lungs were clear Aortic and mitral systolic murmurs were heard over the heart The liver and spleen were not felt The finger nails were brittle, broken and irregular and showed some incurving Rectal examination revealed a few small external hemorrhoidal tags Complete neurologic examination was normal. Orthopedic examination of the spine was normal A thorough gastro-intestinal study failed to reveal any cause for the hemorrhages Gynecologic examination was likewise normal By gastric analysis no free hydrochloric acid was discovered, even after histamine stimulation The red cells numbered 4 86 million, the hemoglobin was 7 3 grams, the mean corpuscular volume 60 $c\mu$, the mean corpuscular hemoglobin concentration 25 per cent, and the icterus index 3

Following the administration of large doses of iron the anemia has gradually disappeared and the patient has regained her strength No further hemorrhages have occurred to date

Hemorrhoids which bled occasionally were present in five of our patients It seemed clear from their histories, however, that the small amount of blood lost in this way could not account for the severe degree of anemia present

Cardio-respiratory system Dyspnea, palpitation, choking sensations and even edema may be encountered In two of Witts' cases, (89) true anginal pain on exertion which disappeared on repair of the anemia, was present These are all symptoms which have come to be associated with anemia of any type

Genito-urinary system Menorrhagia of varying degrees which is not associated with organic pelvic disease, appears to be a symptom of some importance in these patients It was a complaint in 15 per cent of 189 cases (89, 20, 32, 29, 11, 79) for which information on this subject is available but, since many writers have not even mentioned this symptom, its incidence may be exaggerated by this figure In no reports has menorrhagia been considered to be more than, at most, a contributing factor in the development of the anemia Very often this symptom has appeared many years after the onset of symptoms of anemia; in other cases it was not of such severity as would be expected to cause the degree of anemia present In several cases hysterectomy was not followed, even in two or more years, by relief of the anemia and this only took place after iron was given It does not seem, therefore, that in these cases the uterine bleeding is the fundamental

cause of the anemia Haden (32) found that in his patients the abnormal bleeding was relieved when the blood returned to normal under iron therapy Minot emphasizes this feature (57a)

Irregularity of the menstrual flow and amenorrhoea are less common symptoms The latter occurred in five of Witts' 50 cases and in two of our own

In view of the frequency of *renal* disturbance in pernicious anemia (15, 75), it would be of interest to know the state of renal function in this type of anemia Unfortunately the literature affords no information on this subject In four of our patients occasional traces of albumin were found in the urine but, with one exception, no casts or red blood corpuscles were noted on microscopic examination, and the fluctuations in specific gravity were normal Phenolsulphonephthalein tests were carried out in eleven patients Only in the one case above mentioned was the dye excretion below normal (35 per cent) This was a woman of 66 years who showed moderate arteriosclerosis and hypertension

Neurologic system Numbness and tingling in the limbs is not unusual in idiopathic hypochromic anemia This symptom was noted in 17 per cent of 234 cases (89, 21, 32, 57, 17, 11, 59) concerning which information is available, and was even more common in our series (36 per cent) It is noteworthy, however, that this complaint rarely attains the prominence encountered in pernicious anemia In only one of our patients was it a major complaint As Meulengracht (55) has pointed out, the paresthesiae are mild and of a more transitory nature than in pernicious anemia, "reminding one of the acroparesthesiae frequently appearing in the menopause " In one of our patients the numbness was felt in the left side of the chest

Objective neurologic findings are very rare in idiopathic hypochromic anemia Only two cases in which the latter signs were found, have been reported and even in these the signs were by no means unequivocal Witts (89) had a patient with hypochromic anemia, sore tongue and achlorhydria, who complained of increasing weakness of the legs without unsteadiness or paresthesiae The abdominal reflexes and the right ankle jerk were absent Dameshek's patient (17) complained of numbness and tingling of the fingers and toes and was found to have a "definitely positive Babinski" on the left, absent right knee jerk,

some hyperesthesia of the lower extremities but vibratory sensation and all other neurological signs were normal

Physical examination The *appearance* of these patients is often quite characteristic They do not look acutely ill, but appear tired and lifeless, and resigned to a state of chronic invalidism Their fatigued, listless expression is characteristic The pallor is striking The appearance is waxy and bloodless in the more severe cases The color is usually white but not infrequently it is mixed with a light brownish coloring of skin Less commonly, the yellowish pallor of pernicious anemia is simulated In such instances, however, the conjunctivae will not be found icteric and the sclerae are blue or pearly white The hair is often scanty, dry and brittle The skin may be wrinkled to an unusual degree and is inelastic (20)

Equal numbers of our patients were thin, normal and obese Mention has already been made of the frequent similarity in the body build of these patients to the constitutional type described in pernicious anemia

Papillary atrophy of the tongue is common The atrophy may be very striking, but usually it is less marked than in pernicious anemia and it may be limited to the edges of the tongue Atrophy of some degree was noted in 64 per cent of our patients and in 50 per cent of Witts' cases (89) Information on this subject is available concerning a total of 238 cases (89, 20, 32, 17, 29, 11, 73a, 79, 59, 92) Atrophy was noted in 39 per cent

Slight *cardiac* enlargement may be encountered Functional systolic murmurs are very common

The abdominal wall is atonic and inelastic The edge of the *liver* has been felt in a small proportion of cases The *spleen* was palpable in 50 per cent of our cases Of a total series of 255 cases (89, 84, 53, 1, 21, 57, 11, 20, 92), this organ has been felt in 33 per cent The size of the spleen is never very great It has been found to extend at most to three finger-breadths below the costal margin In a number of our cases its edge could not be made out until the patient was turned on her right side With successful treatment the spleen frequently recedes within the costal margin (89)

Kaznelson, Reimann and Weiner (44) have called attention to a peculiar flattening and concavity of the finger-nails, *koilonychia*, which

is sometimes encountered in these patients In extreme examples of this abnormality, the concavity is so marked that a drop of water may be held on the nail Usually the nails of two or three fingers are so affected while the other nails appear dull and lustreless and are longitudinally striated and irregular (fig 3)

Extreme changes in the nails are infrequent but it is common to find less marked modifications and a number of patients, when specifically

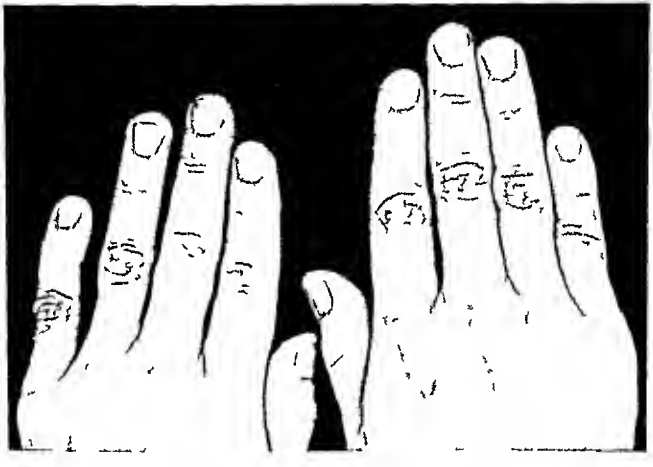

FIG 3 KOILONYCHIA IN IDIOPATHIC HYPOCHROMIC ANEMIA

Note especially the concavity of the nail of the right index finger and the marked longitudinal striations of all the nails

questioned, state that their nails are brittle and break very readily In a number of our cases they have been sore Nail changes were noted in 40 per cent of our patients and in approximately 30 per cent of 137 reported cases (89, 20, 17) in which such observations were made Witts has made the interesting observation that "on cure of the anemia the new nail has the normal contour so that for some time there is a ridge marking the beginning of successful treatment" (89) One of our patients who has now suffered several relapses because of neg

lect of treatment, has stated that the return of anemia is announced, along with weakness and sore tongue, by soreness of the finger-nails

Koilonychia, while no doubt not specific to this disorder is nevertheless a characteristic and interesting symptom It is known that traces of iron are present in all living cells and are necessary for biologic oxidations (82) It has been suggested that the dystrophy of the nails is the result of a poor supply of iron to the germinative cells of the nail root (36, 18)

Complicating or associated conditions In approximately 30 to 40 per cent of cases of idiopathic hypochromic anemia, some associated or complicating disorder has been present Thus 11 of Dameshek's 25 cases were complicated six by recent pregnancy, two by extensive operations on the stomach, and one by dysphagia, one by myxedema and one by beef-tapeworm infestation Among our own 25 cases the following conditions were found in one case each arthritis, rheumatic heart disease, chronic cholecystitis, syphilis, uveitis, dysphagia and gastro-enterostomy The relation of dysphagia to idiopathic hypochromic anemia has already been discussed The significance of repeated pregnancies and of extensive gastric operations will be considered in a later section That some of the other complications above mentioned aggravate the anemia can hardly be doubted, that they are solely responsible for it, seems highly improbable Although they may be removed the anemia persists and, even when the anemia has subsequently been relieved by iron therapy, it often returns when iron is discontinued Mills (57) mentions an interesting case in which myxedema was a complication After both the anemia and the hypothyroidism had been successfully treated by the administration of iron and of thyroid extract, the latter was discontinued The myxedema promptly reappeared but the blood remained normal

THE GASTRIC SECRETION

It was the frequent association of hypochromic anemia with achlorhydria which led Faber to call attention to the condition under discussion In some of the succeeding reports achlorhydria was considered to be a necessarily associated sign of this disease as the name "simple achlorhydric anemia" used by several writers (89, 20, 32) indicates Added experience suggests, however, that achlorhydria is not

as consistent a sign in this disorder as it is in pernicious anemia and even observers like Haden (32) and Meulengracht (55) who have limited their cases to those in which achlorhydria was found by the Ewald test meal, admit that "the achylia is not of the same radical character as in pernicious anemia"

One of the observed points of difference on which all writers agree is that, in some cases, histamine injection is followed by the appearance of free hydrochloric acid although none is secreted in response to an Ewald meal Several writers have included among their cases, patients who secreted small amounts of free hydrochloric acid in response to the Ewald test and a few have observed rare cases which corresponded in every respect to the disorder here considered except that the secretion of hydrochloric acid was found to be normal (83, 17, 11)

Examining the gastric secretion of idiopathic hypochromic anemia in some detail, Davies (21) has called attention to an excessive secretion of mucus and decreased secretion of pepsin The latter was entirely absent in four of his fifteen cases Histamine was found to increase somewhat the total volume of secretion as well as the amount of pepsin and in six cases the pH decreased, with free hydrochloric acid appearing in four instances In contrast to these findings, Davies noted in the gastric secretion of cases of pernicious anemia, no mucus, great diminution or total absence of pepsin secretion, and no change in the volume or pH after histamine stimulation

It is also interesting to note, as further evidence of the incomplete nature of the gastric deficiency in this type of anemia, that Castle and his associates were able to demonstrate the presence of "intrinsic factor" in the gastric secretion of three cases of hypochromic anemia, although in two of these patients it was present in less than the normal amount

It is thus clear that in idiopathic hypochromic anemia the disturbance in gastric secretion is not as grave as is found in pernicious anemia As more cases are observed and the clinical characteristics of this anemia become more clearly defined, it seems that achlorhydria must not be made too rigid a criterion for differentiation and it becomes apparent that a few patients without achlorhydria may be encountered whose symptoms, blood findings, response to treatment, and tendency to relapse when therapy is discontinued, make up a clinical picture in-

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distinguishable from idiopathic hypochromic anemia In classifying our own patients we have been guided by these considerations and have found that the cases could be subdivided on the basis of gastric secretion into four classes

(1) A group in which no free hydrochloric acid was secreted even after histamine stimulation, this was noted in 60 per cent of the cases,

(2) Patients who secreted low or normal amounts of free hydrochloric acid after histamine stimulation although the Ewald meal had been ineffective in eliciting acid (23 per cent),

(3) Cases of hypochlorhydria (Ewald) (8 5 per cent),

(4) Cases in which the secretion of hydrochloric acid seemed to be normal (8 5 per cent)

Including our own patients reports are now available concerning gastric analysis in a total of 334 cases (93a, 84, 53, 1, 20, 32, 57, 55, 18, 29, 11, 73a, 79, 59, 92) In 84 per cent no free hydrochloric acid was found by the Ewald test

THE BLOOD

The blood picture is one of the most characteristic features of this disorder The *erythrocyte count* when considered in relation to the appearance of these patients, is found to be surprisingly high The red cells may even be normal in number and we have encountered values as high as 5 86 million when the hemoglobin and volume of packed red cells were far below normal (table 2, patient M R) In 90 per cent of our patients the red cells numbered between 3 00 and 5 15 million The lowest count was 1 50 million but such a count is very unusual in this type of anemia

The striking deficiency is found in the *hemoglobin* content of the blood This is reduced far out of proportion to the number of red cells and even out of proportion to the volume of packed red cells In 74 per cent of our cases the hemoglobin was 6 to 10 grams per 100 cc of blood (41 to 70 per cent) Values of 6 to 8 grams (41 to 55 per cent) are most often encountered The *volume of packed red cells* was 23 to 35 cc in 80 per cent of our cases

The disproportion between the relatively normal erythrocyte count and the reduction in hemoglobin and in volume of packed red cells can be readily understood when the *blood smear* is examined The

great majority of the red cells are small and poorly filled with hemoglobin, although a few macrocytes and some polychromatophilic cells are frequently encountered Reticulocytes may be normal, or somewhat increased in number The mean *diameter* of the cells is found to be reduced (6 2 to 6 7μ) and the Price-Jones curve has a broadened base and is swung to the left (53, 63) Poikilocytosis is often rather marked Elliptical erythrocytes are almost constantly found These have occasionally been mistaken for sickle cells but true sickling does not occur in fresh preparations of the blood Occasionally small nucleated red cells (microblasts) or normoblasts are seen

The extreme microcytosis and hypochromia are readily demonstrated by the calculation of the mean volume and hemoglobin content of the erythrocytes In our cases when first examined, the *mean corpuscular volume*[1] averaged 65 c μ and in 75 per cent of the patients this ranged between 55 and 74 c μ We have observed values as low as 50 c μ

The *mean corpuscular hemoglobin* is likewise greatly reduced This constant ranged between 15 and 21$\gamma\gamma$ in 70 per cent of the cases and averaged 18$\gamma\gamma$ Unlike the majority of anemias, the mean corpuscular hemoglobin in this type of anemia is reduced even more than the mean corpuscular volume and this becomes manifest when the *mean corpuscular hemoglobin concentration* is calculated (88) This value was markedly reduced in all cases before treatment was instituted, being above 30 per cent only in one instance In 83 per cent of the cases this ranged between 25 and 30 per cent and in a few it was even lower The average value was 27 per cent

Similar information may be derived by the calculation of the *indexes* The volume index is reduced below normal (0 65 to 1 07, average 0 76), the color index even more markedly (0 42 to 0 81, average 0 62) and the saturation index is likewise found to be low (0 64 to 1 00, average 0 80) (32)

The reduction in the mean volume and hemoglobin concentration of the red cells is of considerable assistance in differentiating this from other types of anemia In pernicious anemia and in other macrocytic anemias the mean corpuscular volume is greater than normal and the

[1] The normal range of mean corpuscular volume is 82 to 92 c μ, of mean corpuscular hemoglobin 27 to 31 $\gamma\gamma$, and of mean corpuscular hemoglobin concentration 32 to 36 per cent

mean corpuscular hemoglobin concentration is usually normal In anemias due to blood destruction such as those caused by the malaria parasite and in aplastic anemias there is no significant alteration in the mean volume or hemoglobin content of the erythrocytes In the anemia associated with various infections and toxic processes relatively slight microcytosis and only a slight reduction in mean corpuscular hemoglobin concentration (30 to 32 per cent) is encountered (87a). The very marked microcytosis and hypochromia above described have been found only in idiopathic hypochromic anemia, in the anemia resulting from chronic blood loss, in hookworm disease, and in chlorosis

In some cases increased resistance of the erythrocytes may be noted by the macroscopic *fragility* test but Waugh, using a microscopic technique, has found quite regularly an increased resistance in the lower salt concentrations and increased fragility in the higher concentrations (84)

No evidence of increased *blood destruction* is to be found The icterus index is normal or more commonly it is below normal Urobilin is present in normal or reduced quantities in the urine (55, 32)

There does not appear to be any significant change in the *leucocytes* They may be normal in number but they are often slightly reduced (55). There is some disagreement concerning the occurrence of granulocytopenia and relative lymphocytosis in this type of anemia (32), but it seems that on the whole the differential count is normal (55) The *platelets* have been found normal or very slightly reduced in number Dameshek (18) has, however, reported one case in which the platelets numbered 44,000 and petechial hemorrhages and ecchymoses occurred Minot (57a) has also observed such cases and refers to the efficacy of iron therapy in such instances of thrombopenia as distinguishing them from other types

PATHOLOGY

The sternal *bone marrow*, examined during life, was found by Weiner and Kaznelson (86) to be crowded with normoblasts and, in contrast to pernicious anemia, megaloblasts were entirely absent No significant deviations from the normal in the leucocytes of the bone marrow were observed Similar observations at sternal biopsy have been reported by Dameshek (17) However, Witts (89) found only fatty marrow in the shaft of the tibia in one patient

Only a few autopsies have been reported The bone-marrow was found erythroblastic in one case by Spenson (74), and "red" (humerus) by Kaznelson (44) One of Witts' patients died following transfusion The amount of hematogenous marrow in the shaft of the femur was "unusually great" (89) There is thus little information from which conclusions may be drawn concerning the state of the bone marrow in idiopathic hypochromic anemia The sternal marrow is known to be the last to become hypoplastic and, therefore, whether or not the findings reported at sternal biopsy correctly indicate the general state of the bone marrow must be left for future observations to determine However the finding of polychromatophilia and an increased number of reticulocytes in a number of cases, as well as the quick response to iron therapy, indicates that in many instances at least, the bone marrow is very active and only awaits a supply of iron in order to replace the ghosts of red cells in the circulation with normal ones

In a case which had been characterized by dysphagia, Suzman (78a) found, at autopsy, hyperkeratinization of the epithelium with areas of desquamation and atrophic degeneration of the underlying muscle tissue throughout the tongue, hypopharynx and esophagus The intermuscular nerve plexus (Auerbach) revealed no abnormality The condition was not considered to be inflammatory Faber (25) observed chronic diffuse follicular *gastritis* in one patient who died of intercurrent infection Atrophy of the mucosa of the stomach and intestines has also been reported (one case) by Spenson (74) In the *spleen* of one of Witts' patients "uniform hypertrophy of the reticulo endothelial system, without increase of fibrous tissue, pure hyperplasia of the spleen with no gross alteration in structure," was observed (89) Extreme anemia of the brain and internal organs, fatty degeneration of the liver and kidneys, pulmonary edema, ecchymoses in the small and large bowel, a firm, enlarged spleen, and circumscribed round cell infiltration in the liver and kidneys, as well as red bone marrow in the humerus, were reported in Kaznelson's fatal case (44)

DIAGNOSIS

Typical examples of this disorder are easily recognized once the physician is aware of the existence of such a condition Whether idio-

pathic hypochromic anemia deserves recognition as a disease entity or whether it should be classed as a syndrome will not be discussed at this point, but there can be little debate that, for practical purposes, this disorder should be considered singly No one will dispute this who has encountered patients who have been subjected to fruitless and expensive investigations and ineffective methods of treatment, or have been labelled "psychoneurotic" and given little further sympathy. A number of patients have undergone needless operations, admittedly exploratory or for supposed organic lesions, only to be worse off mentally, physically and financially Treatment is so simple that this disorder should constantly be kept in mind It is "a fruitful cause of chronic invalidism in women" (89)

When such symptoms as long continued weakness and tiredness, sore tongue or sore mouth, dysphagia, vague gastro-intestinal complaints, or moderate menstrual disturbance, are mentioned by a woman 30 to 50 years of age, and on examination no cause for these complaints is found but pallor, and perhaps papillary atrophy of the tongue, functional cardiac murmurs, splenomegaly or irregular, lustreless fingernails are discovered, and the blood examination reveals microcytic, hypochromic anemia, the probable diagnosis is evident The discovery of disturbed gastric secretion affords corroborative evidence but, as has already been discussed, exceptional cases without achlorhydria have been observed In less typical cases, and in women past the menopause, as well as in men, the diagnosis is more difficult and must be made with more caution It should always be kept in mind that a similar blood picture is produced by chronic blood loss, and it is a good rule to search for a source of blood loss in all cases Perhaps the greatest danger that will probably arise as the result of more general recognition of idiopathic hypochromic anemia, is that the conclusion "idiopathic" will be too readily reached

In some patients a source of blood loss may be discovered and it is then important to decide whether the loss of blood is alone the cause of anemia or whether a more fundamental disturbance is present *Menorrhagia* from no well recognized cause occurs in idiopathic hypochromic anemia and frequently disappears on efficient treatment (32, 47a) Even when some possible causes for hemorrhage, such as fibromyomata, are discovered, it does not necessarily follow that this is the

essential cause of the anemia for adequate iron therapy may be followed by cessation or decrease of hemorrhage even when the tumor has not been removed Every physician has encountered patients who have lost a great deal of blood from hemorrhoids and yet develop little or no anemia, while other patients become anemic with much less provocation The discovery of achlorhydria suggests in such instances that there is a more fundamental cause for anemia than blood loss alone In any case it is wise to treat the anemia before undertaking the removal of hemorrhoids or benign pelvic abnormalities As Witts (89) says, "It is more common for anemia to be erroneously attributed to hemorrhoids than for hemorrhoids to be overlooked"

No doubt many, if not all, cases diagnosed as "*pernicious anemia with low color-index*" are instances of idiopathic hypochromic anemia Many symptoms are common to both types of anemia (table 3) but the lack of evidence of increased blood destruction both on physical and laboratory examination, the absence of objective neurologic signs and the microcytic, hypochromic nature of the anemia as distinguished from the macrocytic anemia so characteristic of Addison's anemia, should make differentiation simple

The *gastro-intestinal* complaints encountered in idiopathic hypochromic anemia may lead to some confusion in diagnosis and in not a few instances they have led to the performance of unnecessary operations As distinguished from peptic ulcer, pain is unusual and never periodic, unlike malignancy, the illness is of longer duration, dyspeptic symptoms are not so pronounced, weight loss is relatively slight, and the appearance is not so cachectic In idiopathic hypochromic anemia the gastro-intestinal symptoms are frequently ill-defined and questioning may elicit a story of glossitis and paresthesias

The resemblance of this anemia to *Banti's syndrome* is apparent No doubt some cases formerly classed under this head were instances of idiopathic hypochromic anemia The occurrence of hematemeses and melena in one of our patients has already been mentioned In two of our patients splenectomy had been advised, but they are now well and still possess their spleens When the splenomegaly is relatively slight, signs of portal obstruction are absent and the blood plasma is pale, a therapeutic test with iron may well be undertaken in all cases in which Banti's disease is suspected

Neurasthenia and *psychoneurosis* are common diagnoses in cases of idiopathic hypochromic anemia (89, 55) These patients are often nervous and difficult, but in many cases the anemia is an important contributing factor

Occult tuberculosis, heart disease, infective endocarditis, myxedema, rheumatism, pyelitis, aplastic anemia, leukemia and colitis, are some of the diagnoses which have been made in these cases These conditions should be differentiated without difficulty

TREATMENT

In contradistinction to pernicious anemia, *liver extract* and *desiccated hog's stomach* are valueless in the treatment of idiopathic hypochromic anemia Six of our patients received these therapeutic agents (Liver Extract, Lilly 343, Ventriculin), in doses totaling 36 to 186 vials over periods of 8 to 33 days In the two cases in which treatment was most prolonged (32 and 33 days respectively) the erythrocyte count rose but the hemoglobin remained unchanged and the red cells became smaller in size In another case the mean corpuscular volume decreased while the erythrocyte count remained unaffected In the remaining three cases no alteration whatever occurred in the blood These findings are in conformity with the observations of others (44, 89, 84, 32, 55) McCann and Dye (53) tested in one patient a "secondary anemia" liver fraction but found this ineffective Vanderhoof (79) alone states that liver extract may be of value He employed E 29 (Valentine) with slight success in one case but the results did not in any way compare with the influence of large doses of iron Likewise there is no evidence that whole liver possesses any value that may be compared with that of iron, and fetal calves' liver has likewise had little influence (1)

The beneficial influence of large doses of *iron* in the treatment of idiopathic hypochromic anemia is now well recognized The response to the administration of iron is so consistently observed that, if this does not become manifest within three weeks after treatment has been instituted, the diagnosis may well be questioned There is an almost immediate improvement in the well-being of the patient, and a gain in appetite and in strength which calls to mind the effect of liver therapy in pernicious anemia The normal color gradually returns, numerous vague symptoms as well as more definite complaints disappear and

even such symptoms as menorrhagia may be completely relieved (32, 57a) However, it must be stated that symptomatic relief, while definite in all cases, is not always complete What rôle psychoneurotic factors play in the continuation of some complaints is difficult to estimate but there can be no doubt that these play a large part, for the temperament of the patients frequently, as the result of long-continued ill-health, becomes nervous and difficult

The essentials in treatment are (1) the administration of *adequate amounts* of iron and (2) *continuous treatment* over a period of several months

Preparations employed A great variety of preparations is employed, the one chosen depending partly on the whim of the physician and the idiosyncrasy of the patient Tablets of *ferrous lactate*, 0 5 gram three times a day, were used by Lichtenstein (50) and are recommended by Meulengracht (55) It is necessary that the tablets crumble easily or they may pass through the gastro-intestinal canal intact For the same reason Blaud's pills (*ferrous carbonate*) must be freshly prepared The minimal effective dose of the latter drug is stated to be 3 to 4 grams daily (93) *Reduced iron* is classed among the ferrous compounds as it is converted into ferrous chloride in the stomach The minimum effective dose is 2 to 3 grams daily The metal is most conveniently administered in capsules containing 0 5 to 1 0 gram *Ferric ammonium citrate* is one of the best of the complex ferric compounds This preparation is very soluble The minimum effective dose is 4 to 8 grams daily It may be given in 10 to 20 per cent solution, or, more simply, the patient is asked to dissolve a half-teaspoonful (2 grams) of the scales in water or milk and to take this amount three times daily All these preparations are taken after meals When liquid preparations are used, precautions must be observed not to permit the iron solution to come in contact with the teeth The liquid may be sipped through a glass tube Witts (89) attempted treatment by the *injection* of *iron* but found this method valueless The investigations of Heath et al (36) demonstrate that the parenteral administration of iron is effective if given in adequate dosage but under such conditions it is very toxic They conclude that this method of treatment is undesirable because of the pain produced, as well as for economic reasons

Like Schulten (69), we have found that in some instances *even larger*

doses of iron than are usually recommended, are required Schulten found it necessary to give as much as 6 grams, and in one case 9 grams, of reduced iron It is of interest in this connection that Witts (89) and Mills (57) have reported refractory cases but that we have so far not encountered one This difference may perhaps be explained by the fact that we have given as much as 12 and even 15 grams of ferric ammonium citrate daily

Untoward symptoms have rarely been observed Many patients, chronically constipated, have found relief while taking ferric ammonium citrate Occasionally doses as large as 10 to 12 grams daily have been followed by diarrhoea This usually has been of short duration Hurst (39) has described one patient who suffered from an acute cerebral attack after she had been under treatment at this dosage for three weeks He attributed this to iron poisoning, "iron encephalopathy" One of our patients who received large doses of iron until her blood reached values 25 per cent above normal, developed very severe headaches at that time These ceased when iron was discontinued and the blood returned to normal

When diarrhoea produced by large doses of ferric ammonium citrate has become troublesome, we have often effectively overcome this difficulty while maintaining adequate iron therapy, by replacing some of the ferric ammonium citrate with Blaud's pills

In our experience, the latter preparation has been much less effective than ferric ammonium citrate This may perhaps be explained by the fact that we have taken no trouble to order freshly prepared Blaud's pills and have relied on the stock preparations generally available in drug stores Nevertheless it is worth noting that the actual iron content of Blaud's pills (10 per cent) is less than that of ferric ammonium citrate (17 per cent) and that the number of Blaud's pills (twelve daily) taken by our patients contains only 22 per cent of the amount of iron in three level teaspoonsful of the former preparation Probably the greater efficacy which has been attributed to ferrous iron salts (64) does not make up for this quantitative difference in actual iron content

Influence of iron therapy on the blood The earliest evidence of response which may be discovered in the blood is an increase in the percentage of *reticulocytes* The magnitude of the increase is, roughly, inversely proportional to the degree of anemia as measured by the

hemoglobin The increase in reticulocytes is maximal usually at the fifth to tenth day after the institution of iron therapy It has been pointed out that the peak of the reticulocyte curves is often much flatter than in pernicious anemia but the period of reticulocyte response is much the same as in the latter disease, namely about twelve days (58)

The increase in number of red cells, hemoblogin and volume of packed red cells may be noted in a few days We can not understand Witts' statement that improvement in the first month of treatment is often slight (89), Dameshek (17) states that remission may be noted in a few days, and this has been our experience In our patients, hemoglobin increased at the rate of 0 15 to 0 20 gram per day on the average There was some variation in the rate of increase, but this did not seem to be correlated with the degree of anemia In some the gain was most rapid in the first two weeks of treatment, in other cases the greatest increase took place in the second two weeks

We have frequently observed an increase in the erythrocyte count to six million and more under the influence of iron therapy This polycythemia is, however, only temporary although it may persist for a month or two The red cell count may be above normal even when the hemoglobin and the size and hemoglobin content of the red cells are still far from normal Even the hemoglobin reaches normal values before the mean corpuscular volume and the mean corpuscular hemoglobin concentration, as figure 4 illustrates Thus the red cell count is not a safe guide in estimating the need for further treatment and even the hemoglobin is not altogether reliable Whenever the cooperation of the patient has permitted, we have continued intensive treatment until the mean volume and hemoglobin content of the erythrocytes have reached normal

In table 2 the pertinent data concerning the influence of iron therapy in twelve of our patients have been assembled It is of interest to note the values for mean corpuscular volume and mean corpuscular hemoglobin concentration which were found before treatment and the changes which followed various periods of treatment From a diagnostic standpoint it is worth noting the values which were found after short and incomplete periods of treatment, because it is sometimes necessary to make a diagnosis in a patient who has already received some iron therapy In such cases the corpuscular hemoglobin con-

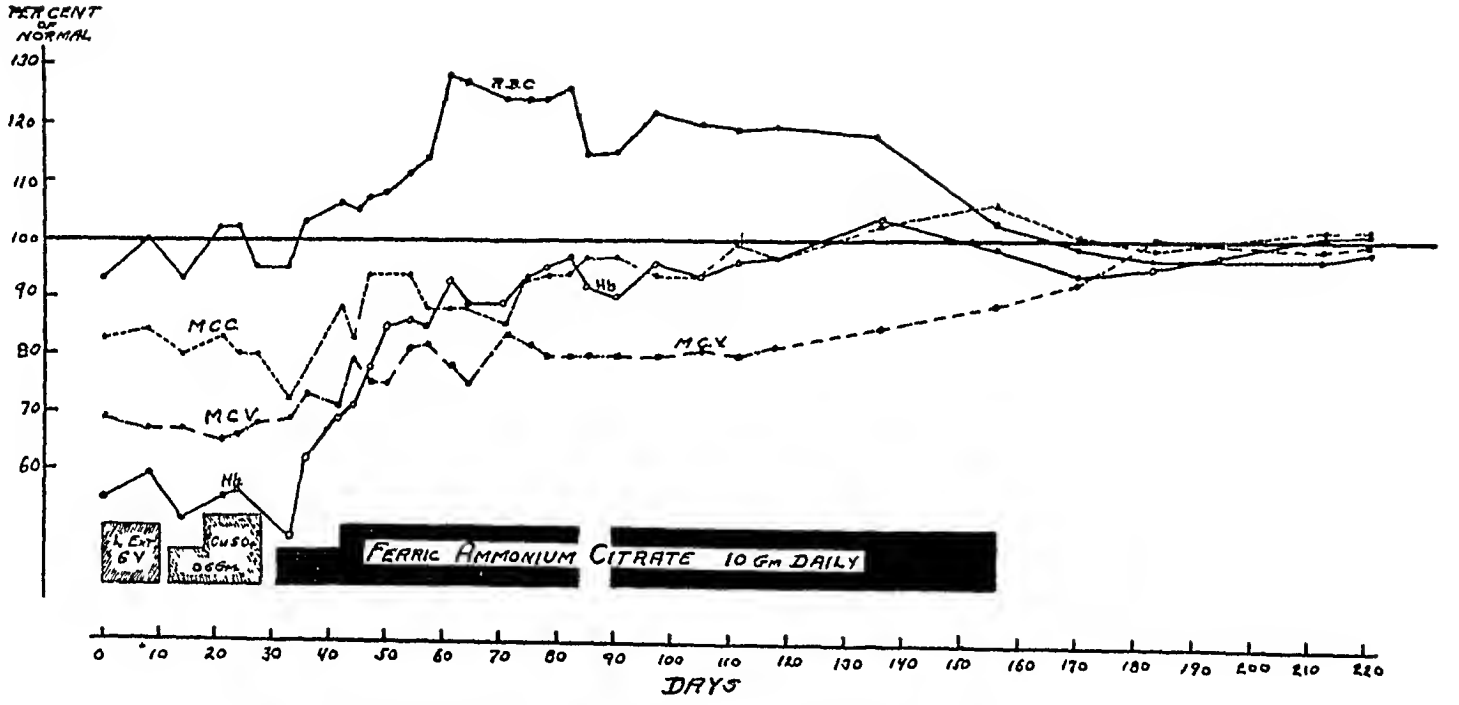

FIG 4 INFLUENCE OF VARIOUS THERAPEUTIC AGENTS ON THE BLOOD IN A TYPICAL CASE OF IDIOPATHIC HYPOCHROMIC ANEMIA

All values are shown in proportion to the normal for the individual Under prolonged treatment with large doses of iron not only the erythrocyte count and hemoglobin but also the mean volume and hemoglobin content of the red cells returned to normal

•———• Number of red cells

○———○ Hemoglobin

— — Mean corpuscular volume

---------- Mean corpuscular hemoglobin concentration

TABLE 2

Influence of iron therapy on the blood

PATIENT	TREATMENT		TOTAL TIME OF TREATMENT	TOTAL AMOUNT OF ACTUAL IRON GIVEN	RED BLOOD CELLS		HEMOGLOBIN		MEAN CORPUSCULAR VOLUME		MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION		DAILY INCREASE IN HEMOGLOBIN	EFFECT OF DISCONTINUING TREATMENT		
	Drug	Daily dose			Before treatment	After	Before	After	Before	After	Before	After	AVERAGE	Number of days	Hemoglobin dropped to	Hemoglobin decrease per day
		grams	*days*	*grams*	*millions*	*millions*	*grams per 100 cc*	*grams per 100 cc*	*cμ*	*cμ*	*per cent*	*per cent*	*grams*		*grams*	*grams*
M R	Iron ammonium citrate	12*	103	77	5 86	5 16	8 5	12 6	54	78	27	31	0 04		Not discontinued	
R M	I A C	10	75	98	4 56	5 11	7 2	12 2	62	75	26	32	0 07	91	8 7	0 04
	Blaud's	4														
F P	I A C	10	55	94	4 31	5 15	8 0	14 2	64	76	29	36	0 11	166	11 0	0 03
	I A C	12	84	120	4 64	5 11	11 0	14 5	76	80	31	35	0 04	89	13 2	0 01
G R	I A C.	10	63	115	4 21	5 18	8 6	14 0	70	84	29	32	0 09	406	No relapse	
R A	I A C	12	112	210	5 12	4 57	7 7	14 2	58	88	26	35	0 06		Not discontinued	
H A	I A C	12	112	198	3 17	5 24	4 9	12 9	62	83	25	30	0 07		Not discontinued—previously had relapsed	
	Blaud's	2														
E Z	I A C	12	117	210	4 51	5 09	7 4	15 3	65	90	25	34	0 07	180	8 0	0 04
O B	I A C	12	115	386	4 55	5 60	7 0	15 1	61	79	25	34	0 07		Not discontinued	
	Reduced Fe	6														
S M	I A C	12	121	216	5 42	5 29	9 0	15 6	63	86	26	35	0 05	293	10 4	0 02
M H	I A C	12	117	169	4 55	4 92	6 7	13 8	59	76	25	37	0 06	182	No relapse	
	Blaud's															
L B	I A C	12	191	390	4 03	5 28	6 6	17 2	68	93	24	35	0 06		Not discontinued	
A T	I A C	10	186	279	4 86	4 64	9 9	14 1	70	86	29	35	0 02	112	No relapse	
Averages		12	112	200	4 60	5 12	7 9	14 4	64	83	27	34	0 06			

* Irregularly

centration may be nearly normal and there may be little microcytosis, but, unless treatment has been entirely adequate, one or both of these values, especially the former, will be found to be lower than normal

Under the influence of adequate iron therapy, polychromatophilic erythrocytes may appear, and an ever-increasing number of normal, orthochromatic red cells is found Price-Jones found these to increase from 12 to 92 per cent and finally they completely replaced the pale cells so characteristic of this type of anemia The mean diameter of the cells in eight cases so studied, increased from 6 48μ to 6 99μ and the distribution curve was shifted to the right (63)

The rate of hemoglobin increase gradually falls after the initial three or four weeks of rapid change It will be noted that the most rapid rates of increase recorded in table 2 generally occurred in the cases treated for a relatively short, but actually inadequate, period of time When the gain in hemoglobin is calculated on the basis of the period of time needed to bring the blood entirely to normal the average daily increment in hemoglobin is reduced from 0 15 to 0 20 gram to 0 05 or 0 07 gram Thus the average weekly gain estimated on the basis of the entire period of intensive treatment, is 0 35 to 0 050 gram hemoglobin

On the basis of the latter value it is possible to make a rough estimate of the length of time required for intensive treatment in a given case Thus in a patient whose hemoglobin is 6 0 grams, intensive treatment will probably be necessary for approximately 16 to 23 weeks whereas for one whose hemoglobin is 9 0 grams treatment for ten to fourteen weeks will be required

Mills (56), and subsequently Waugh (84), and Adamson and Smith (1), have stated that *copper* is of value in at least enhancing the effect of iron All these writers administered iron in the form of Blaud's pills 4 to 6 grams daily together with copper carbonate, 0 004 gram ($\frac{1}{16}$ grain) In several instances this dose of iron was totally ineffective until copper was added

It is of interest that these are the only observers who have found it necessary to supplement iron with copper in the treatment of idiopathic hypochromic anemia In our experience, Blaud's pills in the dosage they employed have not been as effective as ferric ammonium citrate in doses of 6 to 12 grams daily In fact, one of our patients quickly relapsed when Blaud's pills were substituted for ferric ammonium

citrate We have found no need to supplement ferric ammonium citrate with any other drug This may be due to the greater actual amount of iron given in this way and the greater ease with which iron in this form can be absorbed We have given copper alone, in the form of 0 5 per cent solution of copper sulphate 6 to 12 cc daily, to four patients but could observe no beneficial effect In view of the necessity of supplementing Blaud's pills with copper which Mills reports, however, it is of special interest to note that one of our patients who showed no response to copper therapy alone, responded at an average rate of 0 10 gram hemoglobin per day when 1 gram iron ammonium citrate per day was added Since this dose of iron has been found to be ineffective alone, it is possible that the copper received by the patient facilitated its utilization It has been shown to have such an effect in the anemias of infancy (43) and in nutritional anemias in rats (23) We propose to investigate this question further

Little need be said concerning other forms of treatment Witts (89) reports that *transfusion* is of benefit but there seems to be little need, except in emergency, for such a measure when the anemia may be relieved by oral therapy The effects, moreover, are frequently only temporary (84) Administration of *hydrochloric acid* seems to be of no value (89) except in the relief of the gastro-intestinal symptoms which may be due to the achlorhydria

Needless to say, disorders contributing to the ill-health of the patient must be treated However, unless the need is urgent, measures which tax the strength of the patient should be delayed until improvement in the anemia has taken place This particularly applies to operative measures for the treatment of such conditions as bleeding hemorrhoids and pelvic disease Not only is the operative risk lessened in this way, but frequently the bleeding may be found to have diminished or abated after treatment of the anemia

PROGNOSIS AND COURSE

Idiopathic hypochromic anemia leads to chronic, long-continued ill-health but death as a result of the anemia is extremely unusual Only one death which was the consequence of the anemia has been reported (44) The anemia in this case was unusually severe, the hemoglobin being recorded as 15 per cent One of Witts' patients died following

transfusion (89) and a few more have succumbed to intercurrent infections

Unlike pernicious anemia, temporary remissions are uncommon, the anemia gradually progressing or, as far as one can judge by the patients' histories, it may become fixed at a low level beyond which it may not progress

Under the influence of iron therapy, on the other hand, there is rapid alleviation of symptoms and glossitis, acroparesthesias, koilonychia, enlargement of the spleen, menorrhagia, gastro-intestinal and other complaints subside completely or partly (44, 84, 17, 20) Witts (89) estimated that complete cure followed adequate iron therapy in 80 per cent of his patients Mills (57) reported two failures and Meulengracht (55) one, but the latter remarks that in his patients the anemia was complicated by pyuria We have up to the present time not encountered a single patient whose blood has failed to respond to treatment Since we have used exceptionally large doses of a very soluble iron preparation, we are inclined to attribute these results to this cause

Complete symptomatic relief has not followed in every case, however Ready fatigue has persisted in two of our patients in spite of relief of the anemia, although of course this symptom is now less marked than before treatment was instituted It is not easy to determine with any assurance how great a rôle psychoneurotic factors play in the continuation of complaints in some patients, but there can be little doubt that such factors, engendered by long continued ill-health, must play some part

We are inclined to agree with Meulengracht (55) that "the immediate effect appears to be so constant that a retardation or absence of the increase in the hemoglobin value and red cell count in response to iron treatment calls very strongly for a revision of the diagnosis or a search for complications" It might be added that the efficacy of the iron preparation used may be questioned under such circumstances, and that another preparation should be tried That infections and other complications hinder the action of iron in the same way in which they hinder the effect of potent material for pernicious anemia, has been demonstrated by Minot and Heath (58)

The late therapeutic results, however, are in a sense poor With discontinuation of iron therapy, *relapse* is so common that it may be

considered a characteristic of this disorder Meulengracht (55) was able to re-examine 27 of his patients two to six years after treatment was discontinued Although symptomatic relapse did not occur in all the cases, most of the patients proved to be more or less anemic on re-examination A few of these patients had taken some iron during the interval but none had taken large doses persistently Of twelve of our own patients regarding whom information is available, cessation of iron therapy was followed by relapse in nine The time elapsing before relapse was observed, has varied from two to nine months but, since in most instances blood examinations were not made at very frequent intervals after the blood had reached normal, it is quite likely that in these cases relapse occurred earlier than its time of discovery would indicate In only three patients has no relapse occurred after intervals of two, six and thirteen months without iron, respectively

It is thus important to *re-examine* patients who have suffered from idiopathic hypochromic anemia Several observers have advocated the administration of a maintenance dose of a relatively small amount of iron (89, 17) No observations have been reported on the effects of such doses in maintaining at normal the blood of patients who are no longer anemic, but there is no reason to expect that small doses of iron should be effective in such patients when they are known to be ineffective in the same individuals when anemic It seems more logical to do as Meulengracht (55) suggests, namely, to give periodical treatment with large doses of iron Detailed observations regarding maintenance therapy are not available

DEFINITION OF IDIOPATHIC HYPOCHROMIC ANEMIA

At this point it may be useful to attempt to summarize the information which has been presented concerning idiopathic hypochromic anemia This may be considered to be an anemia of unknown etiology occurring especially, but not exclusively, in women in the third to fifth decades of life and one which is characterized by an insidious onset, long duration, symptoms such as are common to all anemias and, in addition, glossitis, stomatitis, dysphagia, paresthesias without objective neurologic findings, and often splenomegaly and koilonychia In the great majority of cases there is evidence of disturbed gastric secretion (achlorhydria) The anemia is characterized by microcytosis

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and hypochromia, ready response to adequate iron therapy and, very frequently, by a tendency to relapse when treatment is discontinued

TERMINOLOGY

As many as fifteen names have been applied to the anemia under discussion [2] It seems to us that in naming this condition, the fundamental characteristics which are encountered in all variants of the clinical picture should be used These seem to be the hypochromic nature of the anemia and the absence of any of the accepted causes for this type of anemia Achlorhydria, as has been pointed out, is not found in all cases and therefore this term should not be used in naming this condition Likewise the term "chlorotic" is better avoided for it implies a relationship with the disease chlorosis which is not generally accepted For these reasons we have used the name idiopathic hypochromic anemia The relation of chlorosis to the anemia under discussion will be considered later

PATHOGENESIS

In any consideration of the pathogenesis of idiopathic hypochromic anemia, the *relationship* of this anemia *to pernicious anemia* becomes a subject of importance Although as regards sex incidence and ultimate outcome, these anemias are quite different, and the distinctly microcytic, hypochromic, non-hemolytic character of idiopathic hypochromic anemia with its spectacular response to iron therapy and resistance to liver therapy distinguishes this disorder as the apparent antithesis of pernicious anemia, in numerous other respects these two types of anemia are quite similar (table 3) In symptomatology they are sometimes indistinguishable Glossitis and paresthesias are symptoms in common They have been described as occurring in individuals of the same constitutional type, idiopathic hypochromic anemia has been found in members of "pernicious anemia families," and a few instances of the transition of one type of anemia to the other, have been recorded

[2] Simple Achlorhydric Anemia, Achylic Chloroanemia, Achylic Chlorosis, Chronic Chlorosis, Late Chlorosis, Chlorotic Anemia, Pseudo-Pernicious Anemia, Hypochromic Anemia with Achlorhydria, Primary Hypochromic Anemia, Idiopathic Hypochromic Anemia, Idiopathic Hypochromemia, Essential Hypochromic Anemia, Chronic Hypochromic Anemia, Hypochromatic Anemia, Erythro-normoblastic Anemia

TABLE 3

Comparison of pernicious anemia and idiopathic hypochromic anemia

	PERNICIOUS ANEMIA	IDIOPATHIC HYPOCHROMIC ANEMIA	
		Similarity to P A	Points of difference
Etiologic features			
Age	Especially 45 to 60 years		Especially 35 to 50
Sex incidence	Approximately equal		Females 96 per cent
Race incidence	Rare in full blooded negroes	Uncommon in full blooded negroes	
Constitutional type	Often characteristic	Often similar to P A type	
Familial incidence	Common	Described, even in P A families	
Symptomatology			
Onset of symptoms	Insidious	Insidious	
Duration	Years	Years	
Character Symptoms of anemia	Characteristic	Characteristic	
Gastro intestinal	Common	Common	
Tongue sore or atrophic	Characteristic	Common, but perhaps less than in P A	
Sore mouth	Uncommon		Not unusual
Dysphagia	Rare		Fairly common
Neurological symptoms	Common and characteristic	Paraesthesias in 18 per cent	
P E Neurological signs	Characteristic		Very rare
Nutrition	Often good	Often good	
Color	Characteristically yellowish pallor		White or waxy pallor (but may be yellowish)
Spleen palpable	30 per cent	33 per cent	
Koilonychia	None		30 per cent
Gastric analysis			
Free hydrochloric acid	Absent in 99 9 per cent	Absent in 84 per cent	
Mucus	Absent		Greatly increased

TABLE 3—*Concluded*

	PERNICIOUS ANEMIA	IDIOPATHIC HYPOCHROMIC ANEMIA	
		Similarity to P A	Points of difference
Gastric analysis—Con'd			
Pepsin	Absent	Absent in 25 per cent, decreased in majority	
Influence of histamine	None		Slight increase in volume, HCl and pepsin
Blood findings			
R B C Number of R B C	Characteristically under 3 5 million		Usually 3 5 to 5 0 million
Hemoglobin	Not proportionately reduced		Very markedly reduced
Size of red cells	Increased (95 to 160 c μ)		Decreased (50 to 80 c μ)
Hemoglobin concentration of red cells	Normal (33 to 37 per cent)		Decreased (22 to 29 per cent)
Nucleated red cells and polychromatophilia	Common in severe cases		Less common
W B C	Leucopenia		Normal or slight leucopenia
Platelets	May be decreased		Normal
Bilirubin in blood plasma	Increased		Normal or decreased
Bone marrow	Megaloblastic		Normoblastic
Course	Remissions and relapses		Remissions rare without treatment
Prognosis	Fatal without treatment		Only 1 death reported
Treatment			
Liver	Excellent		No or little value
Liver extract	Excellent		Valueless
Iron	No value		Very effective
Effect of stopping treatment	Relapse	Relapse	

The familial incidence of idiopathic hypochromic anemia and pernicious anemia has already been discussed The *transition* from microcytic, hypochromic anemia to the macrocytic type is quite rare but several cases of this sort have been described One of the members of Gram's anemic family (fig 2) was found to have typical idiopathic hypochromic anemia at the age of 43 years but ten years later classical pernicious anemia was discovered (30) Witts (89) has described a patient who developed Addison's anemia and subacute degeneration of the cord after she had had "simple achlorhydric anemia" for six years Dameshek (17) cites a similar case In two members of the family reported by Heath (35) an initial microcytosis was changed under iron medication to macrocytosis Witts (89) has described the opposite change in a patient with glossitis, dysphagia and initial megalocytic anemia who subsequently developed microcytic anemia

We have observed a patient who for twelve years has suffered from a chronic anemia associated with glossitis, achlorhydria, splenomegaly and koilonychia The symptoms appeared during her first pregnancy and have been present in varying degrees ever since She came under our observation two years ago, in the sixth month of her seventh pregnancy The anemia which was found to be microcytic and hypochromic in type, failed to respond to intensive treatment with desiccated hogs' stomach and was equally resistant to iron therapy Finally, when the erythrocyte count had fallen to 1 96 million, intensive liver therapy was attempted once again To our surprise, the anemia now became macrocytic (fig 5), the reticulocytes rose to 17 per cent, the anemia rapidly improved and normal spontaneous delivery followed in due course The mean volume of the red cells is now within normal limits but moderate anemia which has resisted further liver and iron therapy, still persists One attack of glossitis followed by diarrhoea has occurred since the stormy episode during the last pregnancy

The relationship of these anemias is particularly emphasized by the regularity with which evidence of *disturbed gastric secretion* is discovered in both Moreover, just as in pernicious anemia, *achlorhydria* is found to *precede* the development of idiopathic hypochromic anemia Achlorhydria was demonstrated in 18 of Meulengracht's cases some time before these patients came under his observation (55) In nine of these cases the gastric defect had been found five to twenty years

TABLE 3—*Concluded*

	PERNICIOUS ANEMIA	IDIOPATHIC HYPOCHROMIC ANEMIA	
		Similarity to P. A.	Points of difference
Gastric analysis—Con'd			
Pepsin	Absent	Absent in 25 per cent, decreased in majority	
Influence of histamine	None		Slight increase in volume, HCl and pepsin
Blood findings			
R. B. C. Number of R. B. C.	Characteristically under 3.5 million		Usually 3.5 to 5.0 million
Hemoglobin	Not proportionately reduced		Very markedly reduced
Size of red cells	Increased (95 to 160 c. μ)		Decreased (50 to 80 c. μ)
Hemoglobin concentration of red cells	Normal (33 to 37 per cent)		Decreased (22 to 29 per cent)
Nucleated red cells and polychromatophilia	Common in severe cases		Less common
W. B. C.	Leucopenia		Normal or slight leucopenia
Platelets	May be decreased		Normal
Bilirubin in blood plasma	Increased		Normal or decreased
Bone marrow	Megaloblastic		Normoblastic
Course	Remissions and relapses		Remissions rare without treatment
Prognosis	Fatal without treatment		Only 1 death reported
Treatment			
Liver	Excellent		No or little value
Liver extract	Excellent		Valueless
Iron	No value		Very effective
Effect of stopping treatment	Relapse	Relapse	

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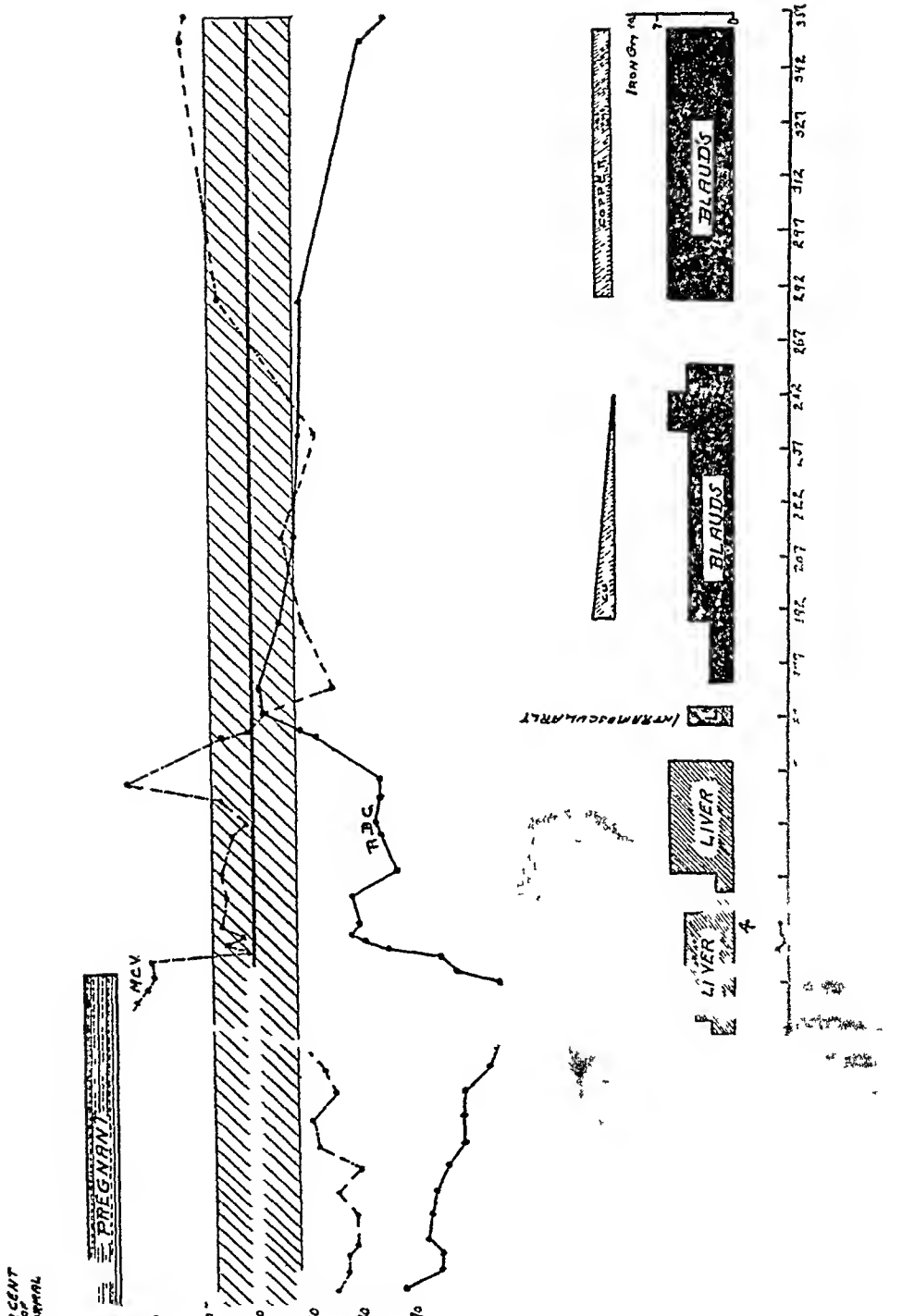
PERCENT OF NORMAL IVO
130
120
110
100
90
80
70
PREGNANT
MCV
RBC
INTRAMUSCULARLY
LIVER
LIVER
BLAUDS
BLAUDS
IRON Gm %
7
0
4
192
207
222
237
252
267
282
297
312
327
342

before, at which time no anemia had been observed It seems also that achlorhydria is the one abnormality which *persists* in spite of successful treatment of the anemia (18)

That defective gastric secretion, usually of many years duration, is the fundamental cause in the development of pernicious anemia is now generally accepted even though the etiologic factors in the production of this gastric disturbance are not known It is argued that in idiopathic hypochromic anemia defective gastric secretion is likewise the essential derangement What has been said about its relationship to pernicious anemia, and the available information concerning the incidence of achlorhydria in idiopathic hypochromic anemia lends support to such an hypothesis

This theory finds further support from another angle An extraordinary feature of idiopathic hypochromic anemia is the large amount of iron needed in treatment In comparison, the amount of iron contained in the whole body, 3 to 3 5 grams, seems infinitesimal Our patients received, on an average, a total of 194 grams of metallic iron, which represents a dose of 1 8 grams daily The daily increment in hemoglobin (0 06 gram) was, in comparison very small indeed (3 3 per cent) That this great discrepancy between amount of iron given and quantity of hemoglobin formed, is due largely to defective absorption of iron from the gastro-intestinal tract, is suggested by the recent observation already quoted, that a dose of metallic iron given parenterally is 30 times as potent as that given orally (36)

The etiologic rôle of defective gastric secretion is further suggested by the number of instances in which hypochromic anemia has followed *extensive gastric operations* The development of pernicious anemia following gastro enterostomy and total gastrectomy has been reported by many observers (19), but it seems that a hypochromic type of anemia occurs even more frequently Among 52 patients, re-examined several years after gastrectomy (Polya), Gordon-Taylor et al (28), discovered anemia in 23 In two patients the color index was above 1 0, whereas in eleven it was 0 6 to 0 3 It is of interest that the anemia was not associated with any symptoms but was discovered through laboratory examination No cause for this anemia was found, but, just as in idiopathic hypochromic anemia, there was evidence of disturbed gastric secretion Hydrochloric acid was demonstrated in only three of the

Anemia does not, however, always follow gastric operations La (47) found no evidence of anemia in 51 cases of partial gastrector It seems likely, as Morley and Roberts suggest (59a) that this differe in the effects of gastrectomy depends on the amount of stomach remo and the consequent influence on gastric secretion and rate of emptyi These investigators found severe anemia three times as common f lowing the Polya gastrectomy as compared with the Schoemaker op ation

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secretion, and if the latter is the primary cause in the development of this anemia, it would be expected that the incidence of achlorhydria, like that of idiopathic hypochromic anemia, is predominant in women This, however, does not seem to be the case The incidence of achlorhydria in nearly 11,000 adults of all ages (46, 16, 8, 80, 34, 49) is approximately 17 0 per cent in females as compared with 12 6 per cent in males It is true that some observations indicate that gastric acidity is usually higher in men than in women (80) and other investigations suggest that achlorhydria becomes more common in women as age advances (34, 40), but these differences do not seem to be sufficient to explain the preponderance of idiopathic hypochromic anemia in women

An additional discrepancy is encountered when the age incidence of this anemia is considered in relation to the age incidence of achlorhydria It is well known that the latter increases in frequency with age Yet, this is not true of idiopathic hypochromic anemia, the predominating age incidence of which is 35 to 50 years Even when recomputed according to the total number of persons of each age group living, the optimal period is about 40 to 50 years (55) It seems, therefore, that an added factor must be considered as playing an etiologic rôle in the development of idiopathic hypochromic anemia

The fact that this anemia develops most often during the period of life when *menstruation and pregnancy* place excessive strain on hemoglobin regeneration, affords a very plausible explanation for the development of anemia when it is presumed that, in contrast to the great majority of women in whom the normal performance of the reproductive functions leads to no ill effects, in these patients there is defective utilization of hemoglobin-building material in the diet and consequently failure to adequately replace the blood lost It is not at all unusual to discover in many cases that the anemia was first noticed during pregnancy and that repeated pregnancies aggravated the original disturbance Adamson (1) has emphasized this point and our own experience supports it In as many as 17 per cent of our patients the onset of symptoms was definitely related to pregnancy As additional evidence favoring this opinion may be cited the infrequency with which this type of anemia is found to commence after the menopause

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from the "physiologic" anemia, in which no significant alterations in the size and hemoglobin content of the erythrocytes takes place, is probably essentially the same disorder as idiopathic hypochromic anemia This seems clear from a study of Strauss' cases (75a), and a number of our own The symptoms are similar to those of idiopathic hypochromic anemia and achlorhydria is very common These cases differ only in that symptoms first became prominent during pregnancy The following patient is a good example

H A (U 21080), a negress 36 years of age, came to the gynecologic dispensary because she felt "bad when the periods ended" The symptoms consisted of nausea and sometimes vomiting In the past two months they had followed the end of menstruation but for a year prior to this they were said to precede the onset of menstrual flow In other respects she had no complaints Loss of blood during menstruation was normal in amount The appetite was moderate and the diet taken was fairly well balanced The patient felt reasonably strong She had lost no weight Gynecologic examination was completely negative but marked pallor of the mucous membranes was noted and she was therefore referred to us

The patient had been in this hospital previously in 1928 with the complaint of shortness of breath of 19 months' duration Questioning revealed the fact that it was during her third pregnancy that these symptoms began and that she had been in excellent health previously Weakness and shortness of breath had continued after the delivery of her child When examined at this hospital in 1928, she was found to be very pale and hypertrophy of the tonsils, systolic cardiac murmurs, and palpable liver and spleen were noted Gastric analysis showed no free hydrochloric acid after an alcohol meal but 10 cc N/10 hydrochloric acid per 100 cc was found following the injection of histamine The red cells were recorded as 1 5 million, the hemoglobin 17 per cent There were marked microcytosis and hypochromia On treatment with Blaud's pills and a Minot and Murphy diet she improved greatly and in 1929 her red cells numbered 5 24 million and the hemoglobin was 86 per cent

As long as the patient continued to take Blaud's pills she remained well She passed through a fourth pregnancy without any apparent difficulty In July 1931, the iron was discontinued Shortly after this, symptoms of weakness gradually returned

There were no additional noteworthy complaints when the patient was seen by us in July, 1932 There was no history of excessive loss of blood even at menstruation The tongue had never been sore and there was no numbness or tingling

Examination revealed marked pallor The patient was thin and of the asthenic habitus The tonsils were hypertrophied, the tongue showed no papillary atrophy There was some doubt about the palpability of the spleen The finger nails showed some flattening and were dull and lustreless The knee jerks were not elicited but otherwise neurologic examination was negative The blood showed 3 17 million red cells, 4 9 grams hemoglobin while the mean corpuscular volume was 62 c μ and the mean corpuscular hemoglobin concentration 25 per cent There was marked anisocytosis with some macrocytes and numerous microcytes Moderate poikilocytosis, marked achromia and moderate polychromatophilia were also noted Leucocytes numbered 7,150 The differential was normal

Treatment with ferric ammonium citrate, 12 grams daily, has been followed by rapid alleviation of the anemia (table 2) and complete relief of symptoms

To restate the *hypothesis* concerning the pathogenesis of idiopathic hypochromic anemia, it may be said that in this anemia, as in pernicious anemia, the fundamental disturbance is defective gastric secretion As a consequence there is faulty utilization or synthesis from the diet of material which is necessary for hemoglobin formation This defect in many cases may be only moderate in degree and for a time little or no anemia may follow As the defect becomes more severe, or as the demands upon the hemoglobin and iron stores of the body become cumulatively greater, anemia appears Perhaps most important in taxing the capacity of the body to cope with this defect, are the demands of menstruation and repeated pregnancies Whereas the blood lost at the menses and the requirements of the foetus are readily met by an individual whose capacity to synthesize hemoglobin from the diet is unimpaired, these demands become too great for those persons whose gastric secretion is defective For this reason idiopathic hypochromic anemia is most common during the later years of the female sexual life, and the lack of such burdens on the hemoglobin forming mechanism explains the rarity of this type of anemia in men Such factors as a diet deficient in foods potent for hemoglobin formation, or excessive menstrual flow, blood loss from hemorrhoids, or dysphagia and consequent lack of food are secondary, alone they do not suffice to explain the development of anemia Indeed these symptoms may have developed as a consequence of the anemia which they serve

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These studies suggest that the lack of free hydrochloric acid and the low total acidity may alone be the fundamental disorder in idiopathic hypochromic anemia Yet, one may ask why evidence of hemoglobin deficiency is so rare in pernicious anemia Again, it is difficult to correlate with this conception the failure of administration of hydrochloric acid to influence the anemia, or to explain the cases of hypochromic anemia, few though they are, which have developed in spite of normal gastric acidity It is true that these are weak objections It may be that much larger amounts of acid than have been employed would have to be administered in order to be of any value, it is admittedly difficult to subsidize the natural gastric secretion Again, it may be that the cases which resemble idiopathic hypochromic anemia in all other respects except that free hydrochloric acid is present in the gastric secretion, should not properly be classed with this disorder Nevertheless, the evidence that absence of hydrochloric acid is the fundamental defect is as yet too weak to be accepted without reserve

Little can be said concerning the *cause of the disturbance in gastric secretion* There is evidence to suggest that in some cases achlorhydria is a constitutional and perhaps a familial and hereditary manifestation (52, 40), or, as Gram suggests (30), instead of achlorhydria, a readily vulnerable gastric mucosa may be inherited Faber (26) has for a long time emphasized the role of gastritis in the production of achlorhydria It must be recalled that achlorhydria is found in association with a number of diseases, many of which, it is presumed, lead to its development Meulengracht (55) pointed out that four of his patients had previously had exophthalmic goitre and, citing the very

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By supplying large amounts of iron to these patients, the barrier to the absorption of iron is in some way effectively scaled and a greedy bone marrow rapidly replaces the ghosts of red corpuscles in the circulation with normal, orthochromatic and efficient erythrocytes The tissues, supplied with adequate amounts of oxygen, and with their iron content renewed, take on normal vigor and function Strength returns, appetite improves, and even such symptoms as glossitis, dysphagia, paresthesias and menorrhagia, as a consequence disappear That the fundamental cause has not been removed by such treatment, however, is shown by the readiness with which relapse occurs when iron therapy is discontinued

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Whether this anemia should be accepted as a specific disease befo more has been learned concerning its causation, must remain a matter opinion It should be pointed out, however, that the recognition pernicious anemia did not await the publication of Castle's illumina ing experiments Nor was that of diabetes mellitus or of Addison disease withheld until insulin was discovered or suprarenal cortic extract made It is thus a matter of definition whether idiopath hypochromic anemia is considered a syndrome or a specific diseas Whether the condition possesses sufficiently well-defined characte istics as regards sex and age incidence, symptomatology, laborato findings, treatment and course, to merit recognition as a specific di ease, must be left for the individual to decide

In any event it seems important, from the practical standpoint, recognize the disorder and to distinguish it from pernicious anemia, ca cinoma, Banti's disease, tuberculosis and the numerous other conditio with which it has been confused, because treatment is so simple ar prognosis is so good Too many patients have been subjected to e pensive, ultra exhaustive and fruitless investigations or have bee called psychoneurotic and given no adequate treatment, for this to b denied

A number of writers have compared idiopathic hypochromic anem to *chlorosis* and have suggested that these conditions are one and th same (1, 10) It may be granted that atypical forms of both cond tions have been encountered which seem indistinguishable Chloros was said to occur occasionally in adult life and the green color wa absent in some patients Yet it must be admitted that typical chlor sis occurred in adolescent girls, it was often characterized by the gree color and it usually disappeared with the onset of pregnancy Idi pathic hypochromic anemia, on the other hand, frequently commence with, and is certainly aggravated by repeated pregnancies Agai glossitis is not mentioned as a symptom of chlorosis (2) Arneth (3 who reviewed the observations on gastric secretion in chlorosis an added some studies of his own, showed that hyperacidity and norma acidity were much more common than anacidity The changes in th blood are identical in the two conditions, but the same blood pictur is also found in chronic blood loss and in hookworm disease Th changes in the blood are the end result and may be produced by

high incidence of achlorhydria in exophthalmic goitre (recently confirmed by Lerman and Means (48)) suggested that in these cases the achlorhydria was brought about by the thyroid disease A critical study of the development of achlorhydria is wanting

IS IDIOPATHIC HYPOCHROMIC ANEMIA A SPECIFIC DISEASE?

Many observers have implied and others have definitely stated that this anemia is a specific disease (89, 17, 57, 79, 57a) Not a few, however, have hesitated to recognize this disorder as a disease entity and these objections have recently found expression in a paper by Bloomfield (10) After enumerating twelve characteristics of idiopathic hypochromic anemia, he points out that the condition is not confined to women, nor to middle age, aberrations in physical findings are to be encountered, gastric anacidity is not constant, and "all sorts of complicating disorders, infections and disabilities are described in various cases" He goes on to point out the similarity of this anemia to chlorosis and concludes that neither disorder represents a truly specific disease, and that idiopathic hypochromic anemia is a syndrome resulting from "some special concatenation of circumstances"

While the variations from the typical picture which have been outlined by Bloomfield are essentially correct, it must be admitted that these are exceptions and not the rule, and that idiopathic hypochromic anemia actually does occur preponderantly in women 30 to 50 years of age, that achlorhydria is encountered in by far the great majority and that the symptomatology is often quite characteristic As has already been discussed, the "complicating disorders, infections and disabilities" which may be associated, do not appear to be the primary disturbance

If idiopathic hypochromic anemia can be conclusively proved to be a disorder which is the result of defective gastric secretion in accordance with the hypothesis already outlined, then it must be considered a specific disease in the same sense as diabetes mellitus receives this title At present, however, our understanding of the process of blood formation is extremely inadequate There is only presumptive evidence that idiopathic hypochromic anemia develops because an individual is unable to meet the demands for hemoglobin or replace the normal loss of blood on account of defective utilization of blood building materials in the diet

Whether this anemia should be accepted as a specific disease before more has been learned concerning its causation, must remain a matter of opinion It should be pointed out, however, that the recognition of pernicious anemia did not await the publication of Castle's illuminating experiments Nor was that of diabetes mellitus or of Addison's disease withheld until insulin was discovered or suprarenal cortical extract made It is thus a matter of definition whether idiopathic hypochromic anemia is considered a syndrome or a specific disease Whether the condition possesses sufficiently well defined characteristics as regards sex and age incidence, symptomatology, laboratory findings, treatment and course, to merit recognition as a specific disease, must be left for the individual to decide

In any event it seems important, from the practical standpoint, to recognize the disorder and to distinguish it from pernicious anemia, carcinoma, Banti's disease, tuberculosis and the numerous other conditions with which it has been confused, because treatment is so simple and prognosis is so good Too many patients have been subjected to expensive, ultra exhaustive and fruitless investigations or have been called psychoneurotic and given no adequate treatment, for this to be denied

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variety of causes Finally, small doses of iron were adequate in the treatment of chlorosis, doses which in idiopathic hypochromic anemia have been shown to be ineffective

SUMMARY

On the basis of 473 cases of a microcytic, hypochromic type of anemia usually associated with achlorhydria, which have been described in the literature, as well as 25 cases personally observed, the etiologic features, symptomatology, laboratory findings, pathology, diagnosis, treatment, course and prognosis, as well as pathogenesis of this anemia are discussed It is defined as an anemia of unknown etiology occurring especially, but not exclusively, in women in the third to fifth decades of life and one which is characterized by an insidious onset, long duration, symptoms such as are common to all anemias and, in addition, glossitis, stomatitis, dysphagia, paresthesias without objective neurologic findings, and often splenomegaly and koilonychia In the great majority of cases there is evidence of disturbed gastric secretion (achlorhydria) The anemia is characterized by microcytosis and hypochromia, ready response to adequate iron therapy and, very frequently, by a tendency to relapse when treatment is discontinued

The evidence so far available suggests that the fundamental disturbance may be defective gastric secretion with faulty utilization or synthesis from the diet of material which is necessary for hemoglobin formation Anemia possibly develops because the demands for hemoglobin are in excess of the capacity of the individual to meet them The requirements of menstruation and repeated pregnancies probably explain the preponderance of this type of anemia in women Such factors as a diet deficient in foods potent for hemoglobin formation, excessive menstrual flow, blood loss from hemorrhoids, or dysphagia and consequent lack of food, are considered secondary aggravating factors and not primary etiologic agents

The advisability of recognizing this condition as a single entity is discussed

BIBLIOGRAPHY

(1) Adamson, J D, and Smith, F H Chronic Chlorosis Canad M A J, 1931, 24, 793

(2) Allbutt, C In Allbutt and Rolleston, A System of Medicine, London, 1912, Macmillan and Company, Ltd, 5, 681

(3) Arneth, J Parallel laufende Magensaft und Blutuntersuchungen bei der Chlorose Deutsche med Wchnschr, 1906, 32, 666

(4) Barkan, G Therapie der Anämien mit grossen Eisengaben Klin Wchnschr, 1923, 2, 1748

(5) Bartlett, C J Family Pernicious Anemia J A M A, 1913, 60, 176

(6) Bauer, F Über die Löslichkeitsbedingungen des Eisens in Säuren als Grundlage für die eisenresorption im Organismus Arch f exper Path u Pharmakol, 1931, 161, 400

(7) Beebe, R T, and Wintrobe, M M The Effect of Hamburg Steak Digested with Normal Gastric Juice in Idiopathic Hypochromic Anemia Arch Int Med (in press)

(8) Bell, J R Notes on a Consecutive Series of 425 Gastric Analyses by the Fractional Method Guy's Hosp Rep, 1922, 72, 302

(9) Bittorf, A Unterernahrung und Krankheiten unter besonderer Berücksichtigung atypischer Formen der perniziosen Anamie München med Wchnschr, 1923, 70, 419

(10) Bloomfield, A L Relations Between Primary Hypochromic Anemia and Chlorosis Arch Int Med, 1932, 50, 328

(11) Bode, O B, and Krumm, G Die einfache achlorhydrische Anamie Folia haemat, 1932, 46, 226

(12) Borgbjaerg, A, and Lottrup, M C Blutuntersuchungen bei der Achylie, speziell mit Rückblick auf die perniziose Anämie Acta med Scandinav 1929, 72, 539

(13) Cameron, J A M Dysphagia and Anaemia Quart J Med, 1928–29, 22, 48

(14) Castle, W B, Heath, C W, and Strauss, M B Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia IV Am J M Sc, 1931, 182, 741

(15) Christian, H A Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests Arch Int Med, 1916, 18, 429

(16) Conner, H M Hereditary Aspect of Achlorhydria in Pernicious Anemia, Study of Gastric Acidity in 154 Relatives of 109 Patients Having Pernicious Anemia J A M A, 1930, 99, 606

(17) Dameshek, W Primary Hypochromic Anemia (Erythro-normoblastic Anemia) Am J M Sc, 1931, 182, 715

(18) Dameshek, W Primary Hypochromic Anemia II Clinical Features J A M A, 1933, 100, 540

(19) Davidson, L S, and Gulland, G L Pernicious Anemia C V Mosby Co, St Louis, 1930

(20) Davies, D T Simple Achlorhydric Anaemia Lancet, 1931, 385

(21) Davies, D T Studies on Achlorhydria and Anaemia Quart J Med, 1931, 24, 447

(22) Einhorn, Max Remarks on Achylia Gastrica and Pernicious Anemia Medical Record, 1903, 63, 321

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BIBLIOGRAPHY

(1) Adamson, J D, and Smith, F H Chronic Chlorosis Canad M A J, 1931, 24, 793

(2) Allbutt, C In Allbutt and Rolleston, A System of Medicine, London, 1912, Macmillan and Company, Ltd, 5, 681

(3) Arneth, J Parallel laufende Magensaft und Blutuntersuchungen bei der Chlorose Deutsche med Wchnschr, 1906, 32, 666

(4) Barkan, G Therapie der Anämien mit grossen Eisengaben Klin Wchnschr, 1923, 2, 1748

(5) Bartlett, C J Family Pernicious Anemia J A M A, 1913, 60, 176

(6) Bauer, F Über die Löslichkeitsbedingungen des Eisens in Säuren als Grundlage für die eisenresorption im Organismus Arch f exper Path u Pharmakol, 1931, 161, 400

(7) Beebe, R T, and Wintrobe, M M The Effect of Hamburg Steak Digested with Normal Gastric Juice in Idiopathic Hypochromic Anemia Arch Int Med (in press)

(8) Bell, J R Notes on a Consecutive Series of 425 Gastric Analyses by the Fractional Method Guy's Hosp Rep, 1922, 72, 302

(9) Bittorf, A Unterernährung und Krankheiten unter besonderer Berücksichtigung atypischer Formen der perniziösen Anämie München med Wchnschr, 1923, 70, 419

(10) Bloomfield, A L Relations Between Primary Hypochromic Anemia and Chlorosis Arch Int Med, 1932, 50, 328

(11) Bode, O B, and Krumm, G Die einfache achlorhydrische Anämie Folia haematol, 1932, 46, 226

(12) Borgbjaerg, A, and Lottrup, M C Blutuntersuchungen bei der Achylie, speziell mit Rückblick auf die perniziöse Anamie Acta med Scandinav 1929, 72, 539

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(14) Castle, W B, Heath, C W, and Strauss, M B Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia IV Am J M Sc., 1931, 182, 741

(15) Christian, H A Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests Arch Int Med, 1916, 18, 429

(16) Conner, H M Hereditary Aspect of Achlorhydria in Pernicious Anemia, Study of Gastric Acidity in 154 Relatives of 109 Patients Having Pernicious Anemia J A M A, 1930, 99, 606

(17) Dameshek, W Primary Hypochromic Anemia (Erythro-normoblastic Anemia) Am J M Sc, 1931, 182, 715

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(21) Davies, D T Studies on Achlorhydria and Anaemia Quart J Med, 1931, 24, 447

(22) Einhorn, Max Remarks on Achylia Gastrica and Pernicious Anemia Medical Record, 1903, 63, 321

[illegible], C A, AND SHERMAN, W C The Action of Copper in Iron Metabolism J Biol Chem, 1932, 98, 309
[illegible], K Achylia gastrica mit Anamie Med Klin, 1909, 5, 1310
[illegible], K Anamische Zustande bei der chronischen Achylia Gastrica Klin Wchnschr, 1913, 50, 958
[illegible], K AND GRAM, H C Relations between Achylia Gastrica and Simple and Pernicious Anemia Arch Int Med, 1924, 34, 658
[illegible], S On Atrophy of the Stomach Lancet, 1870, 2, 78
GILLON-TAYLOR, G, HUDSON, R V, DODDS, E C, WARNER, J L, AND WHITBY, L E H The Remote Results of Gastrectomy Brit J Surg, 1928–29, 16, 641
GRAHAM, G, AND JOHNSON, R S Anaemia with Dysphagia Quart J Med, 1932, 1, 41
GRAM, H. C A Study of the Development of Pernicious Anemia Folia haemat, 1930, 39, 461
[illegible], K Schwere Anamien nach totalen Magenresektionen Klin Wchnschr, 1932, 11, 376
HADEN, R L Simple Achlorhydric Anemia J A M A, 1932, 99, 1398
HARE, D C Simple Achlorhydric Anaemia Treated by Iron Brit M J, 1931, 2, 888
HARTFALL, S J Achlorhydria A Review of 336 Cases Guy's Hosp Rep, 1932, 82, 13
(35) HEATH, C W The Interrelation of Pernicious and Idiopathic Hypochromic Anemia J Clin Investigation, 1932, 11, 808
(36) HEATH, C W, STRAUSS, M B, AND CASTLE, W B Quantitative Aspects of Iron Deficiency in Hypochromic Anemia J Clin Investigation, 1932, 11, 1293
(37) HUNTER, C Analysis of 60 cases of Gastric Anacidity Associated Mainly with Chronic Diarrhoea and Pernicious Anemia Canad M A J, 1923, 13, 38
(38) HUPST, A F The Plummer-Vinson Syndrome Guy's Hosp Rep, 1926, 76, 426
(39) HURST, A F A Case of Iron Encephalopathy Guy's Hosp Rep, 1931, 81, 243
(40) HURST, A F Achlorhydria and Achylia Gastrica and their Connexion with the Addison's Anaemia—Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anaemia Quart J Med, 1932, 25, 157
(41) IVY, A C, MORGAN, J E, AND FARRELL, J I Effect of Total Gastrectomy Surg Gynec & Obst, 1931, 53, 611
(42) JONES, A M, AND OWEN, R D Dysphagia Associated with Anemia Brit Med J, 1923, 1, 256
(43) JOSEPHS, H Treatment of Anemia of Infancy with Iron and Copper Bull Johns Hopkins Hosp, 1931, 49, 246
(44) KAZNELSON, P, REIMANN, F, UND WEINER, W Achylische Chloranamie Klin Wchnschr, 1929, 8, 1071
(44a) KEEFER, C S Personal communication
(45) KELLING, G Statistisches über Salzauremangel in Magen Arch f Verdauungskr, 1909, 15, 568
(46) KELLY, A B Spasm at the Entrance to the Oesophagus J Laryng and Otol, 1919, 34, 285
(47) LAKE, N C The Later Results of Partial Gastrectomy Lancet, 1928, 2, 268

(48) Lerman, J , and Means, J H The Gastric Secretion in Exophthalmic Goitre and Myxoedema J Clin Investigation, 1932, 11, 167
(49) Lerman, J , Pierce, F D , and Brogan, A J Gastric Acidity in Normal Individuals J Clin Investigation, 1932, 11, 155
(50) Lichtenstein, A Haematologic Studies of Premature Infants in the Early Years of Life, with Special Reference to Anaemic Conditions Jahrb f Kinderh , 1918, 88, 287
(51) Maclachlan, W W G , and Kline, F M The Occurrence of Anemia in Four Generations Am J M Sc , 1926, 172, 533
(52) Martius, F Achylia Gastrica, Leipzig, 1897 Med Klin , 1916, 12, 481
(53) McCann, W S , and Dye, J Chlorotic Anemia with Achlorhydria, Splenomegaly, and Small Corpuscular Diameters Ann Int Med , 1931, 4, 918
(54) Mettier, S R , and Minot, G R The Effect of Iron on Blood Formation As Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia Am J M Sc , 1931, 181, 25
(65) Meulengracht, E Simple Achylic Anemia Acta med Scandinav , 1932, 78, 387
(56) Mills, C S The Treatment of Idiopathic (Hypochromic) Anemia with Iron and Copper Canad M A J , 1930, 12, 175
(57) Mills, C S Idiopathic Hypochromemia Am J M Sc , 1931, 182, 554
(57a) Minot, G R Idiopathic Hypochromic Anemia Emmanuel Libman Anniversary Volume, 1932, International Press, New York
(58) Minot, G R , and Heath, C W The Response of the Reticulocytes to Iron Am J M Sc , 1932, 183, 110
(59) Moersch, H J , and Conner, H M Hysterical Dysphagia Arch Otolaryng , 1926, 4, 112
(59a) Morley, J , and Roberts, W M The Technique and Results of Partial Gastrectomy for Gastric Ulcer Brit Jour Surgery, 1928, 16, 239
(60) Moore, H Clinical Study of Achlorhydria Brit M J , 1932, 1, 363
(60a) Nolen, W Geneesk Bladen, 1925, 24, 325 (Quoted in Meulengracht (55))
(61) Patek, A J Family Pernicious Anemia J A M A , 1911, 56, 1315
(62) Paterson, D R A Clinical Type of Dysphagia J Laryng and Otol , 1919, 34, 289
(63) Price Jones, C The Red Cells in Microcytic Anaemia J Path and Bact , 1932, 35, 759
(64) Reimann, F , and Fritsch, F Klinische und experimentelle Untersuchungen über die Bedeutung des in der Nahrung enthaltenen Eisen Ztschr f klin Med , 1932, 120, 16
(65) Riecker, H H The Relation of Available Iron to Acid and Alkaline Diets J Clin Investigation, 1931, 10, 657
(66) Ryle, J A A Case of Oesophageal Spasm with Severe Anemia Guy's Hosp Rep , 1927, 77, 33
(67) Salvesen, H A Simple Achylic Anemia Norsk mag f laegevidensk , 1932, 93, 817
(68) Schneider, J P , and Carey, J B The Clinical Significance of Primary Achlorhydria J A M A , 1928, 91, 1763
(69) Schulte, H The Treatment of Hypochromatic Anemia with Large Doses of Reduced Iron München med Wchnschr , 1930, 77, 355

(70) SCHULTEN, H Essential Hypochromic Anemia (Achylic Chlorosis) and its Relations to Pernicious Anemia Munchen med Wchnschr, 1932, 79, 665
(71) SEPPANEN, A Zur Frage der Pathogenese der hypochromen Anamie, Acta med Scandinav, 1929, 34, 126
(72) SINKLER, W, AND ESHNER, A A Three Cases of Essential Anemia in One Family—Father and Two Daughters Am J M Sc, 1896, 112, 287
(73) SONNE, C (quoted in Meulengracht) Hospitalstid, 1920, 63, 713
(74) SPENSON, H (quoted in Witts, 1930) Ugesk f laeger, 1926, 32, 743
(75) STIEGLITZ, E J Disturbances of Renal Function in Pernicious Anemia Arch Int Med, 1924, 33, 58
(75a) STRAUSS, M B Chlorotic Anemia of Pregnancy Am J M Sc, 1930, 180, 818
(76) STRAUSS, M B Observations on the Etiology and Treatment of Anemia in Pregnancy J Clin Investigation, 1932, 11, 809
(77) STRAUSS, M B, AND CASTLE, W B Studies of Anemia in Pregnancy I Gastric Secretion in Pregnancy and the Puerperium Am J M Sc, 1932, 184, 655
(78) STRAUSS, M B, AND CASTLE, W B Studies of Anemia in Pregnancy II The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation during Pregnancy Am J M Sc, 1932, 184, 663
(78a) SUZMAN, M M Syndrome of Anemia, Glossitis and Dysphagia Arch Int Med, 1933, 51, 1
(79) VANDERHOOF, D, AND DAVIS, D Anemia of the Microcytic Type in Middle-aged Women Am J M Sc, 1932, 184, 129
(80) VANZANT, F R, ALVAREZ, W C, EUSTERMAN, G B, DUNN, H L, AND BERKSON, J The Normal Range of Gastric Acidity from Youth to Old Age Arch Int Med, 1932, 49, 345
(81) VINSON, P P Hysterical Dysphagia Minnesota Med, 1922, 5, 107
(82) WARBURG, O Iron, the Oxygen Carrier of Respiratory Ferment Science, 1925, 66, 575
(83) WATKINS, C H Classification of Idiopathic Secondary Anemia Proc Staff Meet, Mayo Clin, 1929, 4, 19
(84) WAUGH, T R Hypochromic Anemia with Achlorhydria Arch Int Med, 1931, 47, 71
(85) WEINBERG, F Der Blutbefund bei der Konstitutionellen Achylia Gastrica Ztschr f angew Anat u Konstit, 1920, 6, 289
(86) WEINER, W, AND KAZNELSON, P Ueber die Zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth Folia haemat, 1926, 32, 233
(87) WINTROBE, M M Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles Proc Soc Exper Biol and Med, 1930, 27, 1071
(87a) WINTROBE, M M The Classification and Treatment of Anemia on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles I Accuracy of Methods, Normal Values, and Physiologic Variations in the Size and Hemoglobin Content of Red Cells II The Types of Anemia, and the Changes in the Size and Hemoglobin Content of the Erythrocytes in *Response to Various Modes of Therapy* (*In Press*)
(88) WINTROBE, M M The Size and Hemoglobin Content of the Erythrocyte J Lab and Clin Med, 1932, 17, 899

(89) Witts, L J Simple Achlorhydric Anemia Guy's Hosp Rep , 1930, 80, 253
(90) Witts, L J Late Chlorosis Guy's Hosp Rep , 1931, 81, 205
(91) Witts, L J Simple Achlorhydric Anemia and Allied Forms of Anemia Practioner, 1931, 127, 439
(92) Witts, L J The Syndrome of Glossitis, Dysphagia and Anemia Guy's Hosp Rep , 1931, 81, 193
(93) Witts, L J The Therapeutic Uses of Iron Proc Roy Soc Med , 1931, 24, 7
(93a) Witts, L J Chronic Microcytic Anaemia Brit M J , 1931, 2, 883
(94) Witts, L J The Constitutional Factor in Diseases of the Blood Practioner, 1932, 129, 450

(70) SCHULTEN, H Essential Hypochromic Anemia (Achylic Chlorosis) and its Relations to Pernicious Anemia Munchen med Wchnschr, 1932, 79, 665
(71) SEPPANEN, A Zur Frage der Pathogenese der hypochromen Anamie, Acta med Scandinav, 1929, 34, 126
(72) SINKLER, W, AND ESHNER, A A Three Cases of Essential Anemia in One Family—Father and Two Daughters Am J M Sc, 1896, 112, 287
(73) SONNE, C (quoted in Meulengracht) Hospitalstid, 1920, 63, 713
(74) SPENSON, H (quoted in Witts, 1930) Ugesk f laeger, 1926, 32, 743
(75) STIEGLITZ, E J Disturbances of Renal Function in Pernicious Anemia Arch Int Med, 1924, 33, 58
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(78) STRAUSS, M B, AND CASTLE, W B Studies of Anemia in Pregnancy II The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation during Pregnancy Am J M Sc, 1932, 184, 663
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(79) VANDERHOOF, D, AND DAVIS, D Anemia of the Microcytic Type in Middle-aged Women Am J M Sc, 1932, 184, 129
(80) VANZANT, F R, ALVAREZ, W C, EUSTERMAN, G B, DUNN, H L, AND BERKSON, J The Normal Range of Gastric Acidity from Youth to Old Age Arch Int Med, 1932, 49, 345
(81) VINSON, P P Hysterical Dysphagia Minnesota Med, 1922, 5, 107
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(84) WAUGH, T R Hypochromic Anemia with Achlorhydria Arch Int Med, 1931, 47, 71
(85) WEINBERG, F Der Blutbefund bei der Konstitutionellen Achylia Gastrica Ztschr f angew Anat u Konstit, 1920, 6, 289
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(88) WINTROBE, M M The Size and Hemoglobin Content of the Erythrocyte J Lab and Clin Med, 1932, 17, 899

(7) [illegible] J. Simple Acetylenic Acetals. Chem. & Ind. [illegible] 84, 85.
(8) [illegible] J. Late Chemical. Chem. & Ind. Rev., 3, 84, 245.
(9) [illegible] J. Simple Acetylenic Acetals and Their Reactions. Tetrahedron, 2, 12, 459.
[illegible], L. J. The Synthesis of Geraniol. Terpenoids and Related. Chem. Ind. Rev., 2, 81, 193.
(11) [illegible] L. J. The Terpenoids Overall [illegible]. Proc. Roy. Soc. Med., 3, [illegible].
(12) [illegible] L. J. Chemical Microscopy. Academic Press, N.Y., [illegible].
(13) [illegible] L. J. The Constituents and Nature of Essential Oils. Tetrahedron, 1958, 12, 45.

(70) SCHULTEN, H Essential Hypochromic Anemia (Achylic Chlorosis) and its Relations to Pernicious Anemia Munchen med Wchnschr, 1932, 79, 665
(71) SEPPANEN, A Zur Frage der Pathogenese der hypochromen Anamie, Acta med Scandinav, 1929, 34, 126
(72) SINKLER, W, AND ESHNER, A A Three Cases of Essential Anemia in One Family—Father and Two Daughters Am J M Sc, 1896, 112, 287
(73) SONNE, C (quoted in Meulengracht) Hospitalstid, 1920, 63, 713
(74) SPENSON, H (quoted in Witts, 1930) Ugesk f laeger, 1926, 32, 743
(75) STIEGLITZ, E J Disturbances of Renal Function in Pernicious Anemia Arch Int Med, 1924, 33, 58
(75a) STRAUSS, M B Chlorotic Anemia of Pregnancy Am J M Sc, 1930, 180, 818
(76) STRAUSS, M B Observations on the Etiology and Treatment of Anemia in Pregnancy J Clin Investigation, 1932, 11, 809
(77) STRAUSS, M B, AND CASTLE, W B Studies of Anemia in Pregnancy I Gastric Secretion in Pregnancy and the Puerperium Am J M Sc, 1932, 184, 655
(78) STRAUSS, M B, AND CASTLE, W B Studies of Anemia in Pregnancy II The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation during Pregnancy Am J M Sc, 1932, 184, 663
(78a) SUZMAN, M M Syndrome of Anemia, Glossitis and Dysphagia Arch Int Med, 1933, 51, 1
(79) VANDERHOOF, D, AND DAVIS, D Anemia of the Microcytic Type in Middle-aged Women Am J M Sc, 1932, 184, 129
(80) VANZANT, F R, ALVAREZ, W C, EUSTERMAN, G B, DUNN, H L, AND BERKSON, J The Normal Range of Gastric Acidity from Youth to Old Age Arch Int Med, 1932, 49, 345
(81) VINSON, P P Hysterical Dysphagia Minnesota Med, 1922, 5, 107
(82) WARBURG, O Iron, the Oxygen Carrier of Respiratory Ferment Science, 1925, 66, 575
(83) WATKINS, C H Classification of Idiopathic Secondary Anemia Proc Staff Meet, Mayo Clin, 1929, 4, 19
(84) WAUGH, T R Hypochromic Anemia with Achlorhydria Arch Int Med, 1931, 47, 71
(85) WEINBERG, F Der Blutbefund bei der Konstitutionellen Achylia Gastrica Ztschr f angew Anat u Konstit, 1920, 6, 289
(86) WEINER, W, AND KAZNELSON, P Ueber die Zellige Zusammensetzung des Knochenmarkes nach Erfahrungen mittels der Sternalpunktion nach Seyfarth Folia haemat, 1926, 32, 233
(87) WINTROBE, M M Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles Proc Soc Exper Biol and Med, 1930, 27, 1071
(87a) WINTROBE, M M The Classification and Treatment of Anemia on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles I Accuracy of Methods, Normal Values, and Physiologic Variations in the Size and Hemoglobin Content of Red Cells II The Types of Anemia, and the Changes in the Size and Hemoglobin Content of the Erythrocytes in Response to Various Modes of Therapy (In Press)
(88) WINTROBE, M M The Size and Hemoglobin Content of the Erythrocyte J Lab and Clin Med, 1932, 17, 899

Physical Chemistry of Living Tissues and Life Processes

As Studied by Artificial Imitation of Their Single Phases

By

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A LIMITED CONSIDERATION OF CERTAIN ASPECTS OF ACUTE INFECTION OF THE RESPIRATORY TRACT[1]

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In expressing my appreciation of the honor of being chosen to deliver the Thayer Lectures I must at the same time acknowledge a very particular and personal debt both to the spirit of this foundation and to Dr Thayer who has for so many years been my teacher and friend I have chosen for my subject the complicated question of acute infection of the respiratory tract, not with the intention of collecting all the known facts but rather of suggesting the operation in these affections of certain interdependent mechanisms the individual exploration of which I consider of great importance

LECTURE I

Many years have elapsed since Flugge first drew attention to the probable importance in the transmission of infections of the respiratory tract of droplets expelled into the air during talking, coughing or sneezing During these same years infectious diseases of the alimentary canal such as dysentery and typhoid fever have so diminished in incidence as almost to have become rarities in the general hospitals of well organized communities The discovery that intestinal infections are commonly spread through the medium of contaminated water and food and the control of the purity of these necessities have brought about a great diminution in the incidence of intestinal diseases In these conditions it has been possible in a relatively simple manner to check the disease in question by breaking the line of communication Unfortunately, infection of the respiratory apparatus is spread for the most part directly from individual to individual by the necessary

[1] Two lectures delivered under the William Sydney Thayer and Susan Reed Thayer Lectureship in Clinical Medicine of the Johns Hopkins University, Baltimore, Maryland March 22–23, 1932

and continuous contacts of human life At present there is not discernible any tendency of acute infection of the respiratory tract to diminish in incidence or in the extent of its geographical distribution It is obvious that if science could bring this type of infection within the sphere of effective public health control great benefit would accrue to humanity In attempting to solve a problem of so complex a nature it is necessary to study carefully, patiently and with a determination not checked by years of apparently fruitless effort, the character and succession of events which are manifest in outbreaks of the diseases under investigation Only by such intensive study will the points of vulnerability in this most strongly intrenched system of diseases be brought into the light of human understanding and perhaps within the scope of successful attack by the forces of preventive medicine

The chief portal of entry of infectious agents into the human body has at all times been the respiratory tract This is readily understandable if we bear in mind that this physiological system is continuously open to all floating matter in the air That it is partially protected by sticky mucous membranes lining tortuous passages, by aggregations of lymphatic tissue, by the ciliary movements of tracheal and bronchial mucosa is true, but one has only to examine the lungs and regional lymph nodes to discover how much foreign material penetrates the protective barriers and reaches the deeper tissues Furthermore, parasitic organisms seem to have evolved special mechanisms by which they are enabled to penetrate and set up pathologic processes at all levels of the respiratory tract from the naso-pharynx to the ultimate air cells

Pathogenic microorganisms gaining entrance to the body by way of the respiratory apparatus in general fall into two large groups In the first group belong the great number of disease producing agents that find only temporary lodgment in the respiratory tract where they may induce for a longer or shorter time relatively insignificant manifestations of inflammation, and thence pass rapidly to more distant localities or throughout the body, to produce their characteristic lesions in organs remote from the respiratory system Types of such diseases are measles, epidemic cerebrospinal meningitis, poliomyelitis, and many others In certain other pathologic conditions there may be first a conspicuous inflammatory disease of the air passages, to be

followed later at varying intervals by specialized types of lesions in organs not directly connected with the respiratory tract Important examples of diseases of this character are scarlet fever, rheumatic disease, and acute hemorrhagic nephritis In the true respiratory diseases the inflammatory process is most evident and continuous in the respiratory tract itself and consists for the most part in catarrhal or suppurative inflammation of the mucous membranes and tissues of the upper and deep respiratory tract In these lectures I propose to discuss principally certain important examples of this latter type of respiratory disease

The most frequent of all the diseases of the respiratory organs is the common cold In fact, this malady is the most widespread and has the highest incidence of any infectious disease from which human beings suffer For example, epidemiological studies indicate that on the average every man, woman, and child in the United States experiences about two and a half colds each year Susceptibility appears to be practically universal and continuous from infancy to old age The symptoms are referable to a catarrhal inflammation of the mucous membranes of the naso pharynx, oro pharynx, larynx, trachea and paranasal sinuses, and are so well known as not to require description The total duration of the disease in its pure form is from three to five days and the clinical manifestations are usually mild However, the occurrence of the malady in this simple form is comparatively rare and there almost always takes place more or less secondary infection with microorganisms probably not responsible for the initiation of symptoms These complications, if they may be called such, consist in inflammation of the paranasal sinuses which may become suppurative, mucopurulent tracheitis and bronchitis and occasionally varying degrees of inflammation of the Eustachian tube and middle ear The bacteria associated with these inflammatory processes are the common potential pathogens, pneumococcus, streptococcus, staphylococcus, and H influenzae that are rarely absent during the winter months from the upper respiratory tracts, even of healthy individuals Such manifestations of cooperative activity on the part of agents causing infection of the respiratory organs illustrate the most important and significant pathologic effect of the common cold and are clearly apparent in the sequence of events characteristic of respiratory infection in general

Study of the epidemiology of the common cold is particularly interesting in this regard. Colds are of world-wide distribution but probably are much more frequent in temperate climates where temperature and weather conditions are extremely variable However, outbreaks occur even in the tropics and the extreme north when populations in these localities are exposed to infection from casual visitors from foreign communities where epidemics of colds are frequent occurrences Colds in tropical regions may be rather mild in character, probably because of the absence in these areas of a wide distribution of the common secondary agents which are responsible for much of the severer symptomatology observed in temperate climates

Investigation of the common cold in representative population groups shows the high morbidity rate of this infection to be cyclic in character The peaks of incidence are three in number and occur in the early fall months, September and October, the mid-winter months, January and February, and the spring months, April and May The character of the different outbreaks varies in respect to severity The spring one is mild as a rule, whereas there appears to be a progressive increase in seriousness particularly of secondary infections of the respiratory tract as the winter advances into spring For example, the number of infections sufficiently severe to cause absenteeism from work is much larger during the January outbreak of colds than during the October outbreak

Observations by Kneeland and Dawes (1) may indicate a possible explanation of this phenomenon These investigators kept the infant population of a foundling home under continuous observation for a number of years in order to study the character of the respiratory infection in such a group and its relationship to the distribution of the common pathogenic organisms of the upper respiratory tract Cultures were made at frequent intervals from the noses and throats of these individuals and the variety and relative number of potentially pathogenic organisms were recorded In addition changes in sensitivity of the skin reaction to the products of representative strains of bacteria were investigated throughout the period of study A record was also kept of the number and character of all acute infections of the respiratory tract experienced by the group under observation Simple upper respiratory infections not accompanied by fever and severe consti-

tutional reaction were classified as colds Serious infections requiring isolation from the general group and manifesting fever and pronounced constitutional reaction were classified as grippe or influenza or if there was obviously involvement of the parenchyma of the lung, as pneumonia During the period that this community was under observation a number of interesting pbenomena were observed

There occurred the usual cyclic outbreaks of acute upper respiratory infection previously noted in the population at large In the early fall the percentage of individuals giving significantly positive reactions in the skin to the various bacterial products used was relatively low, approximately 15 per cent As the winter progressed the positive skin reactions became more frequent and the intensity of the reactions increased until in the late spring 85 per cent of the group under observation gave positive skin reactions to one or other of the bacterial products employed in the test This increased tendency to a positive skin reaction has been interpreted as indicating increasingly frequent and widespread infection with the organisms pneumococcus, streptococcus, and H influenzae whose products were used in making the skin tests While we are unable to say that there is not a spontaneous tendency to an intensified reactivity of the skin under the conditions of the study, we believe that any such tendency is greatly promoted b, the actual experience of infection itself As a rule individuals suffering from the greatest number of infections and those harboring the pathogenic organisms for the longest period of time were found to manifest the most strongly positive skin reactions

Tbe incidence, distribution and type of pathogenic organism found by culture varied from time to time During one year there was for a limited period of time a very high carrier rate of H influenzae On the other hand, during the succeeding year, the carrier rate of pneumococcus rose in one group during a short period of time to the extremely high figure of 95 per cent It is of exceedingly great interest tbat throughout the periods when tbere was a widespread distribution of pathogenic organisms the expected incidence of increased diagnoses of common cold did not occur but was replaced by a very conspicuous rise in the number of diagnoses of grippe, influenza and pneumonia On the other hand, when the distribution of pathogenic organisms was relatively limited, the number of diagnoses of common cold rose

during the expected period to a high figure and there were correspondingly few diagnoses of grippe, influenza and pneumonia

Although the interpretation of these observations is not entirely clear, it seems not unlikely that as a consequence of the repeated cycles of common cold throughout the respiratory year which may be considered as running from September to June, an increasing opportunity is afforded the potential and frequently secondary pathogens of the respiratory tract to cause infection As a result of this, distribution is promoted and virulence perhaps enhanced, these features becoming increasingly important as the year progresses through the cold winter weather to the warmer temperatures of early summer Though these may be but a small part of the total influences involved, nevertheless, this type of associated activity makes it seem probable that epidemics of certain of the severer forms of respiratory infection may result from the coincidence of the outbreak of the common cold with a period of widespread distribution and increased virulence of the well recognized pathogenic organisms of the upper respiratory tract The very illuminating studies and discussions of Theobald Smith on this and kindred phenomena lend strong support to this point of view

Another important disease of the respiratory tract of widespread distribution and of frequent occurrence is epidemic influenza So much has been written about this disease that it is not possible for me to consider thoroughly the numerous studies of it that have been made during the past forty years I should like, however, to draw attention to certain aspects of this infection that are pertinent to the present discussion The disease has certain features that make us believe that it may be closely related in its nature to the common cold The portal of entry is believed most commonly to be the upper respiratory tract and the chief site of the inflammatory reaction seems to be located in the organs of respiration The clinical characteristics of the disease observed during a typical epidemic outbreak are, however, varied and confusing There are in general three principal types of the disease that commonly manifest themselves during epidemic periods First, there is a mild catarrhal inflammation of the upper respiratory tract and trachea without pronounced constitutional reaction and fever and characterized by irritation of the nose and throat Complications as a rule are not severe and there is no prolonged aftermath of depression

and lassitude This type of the disease resembles so closely the common cold that it cannot be distinguished from it and whether it is true influenza or not is of course open to question At all events, during outbreaks in which typical instances of influenza are occurring, a large proportion of acute respiratory disease is of the type just described In the second type of influenza the conspicuous clinical features of the disease are fever of considerable degree and duration, profound prostration and intense general malaise There may be a complete absence of signs of acute inflammation of the respiratory organs Recovery and convalescence are accompanied by prolonged depression and instability of the vasomotor apparatus The severity of the constitutional reaction and the lack of local manifestations suggest the possibility of a general infection There has, however, been no conclusive proof as yet that in this form of influenza the etiological agent gains access to the circulating blood Many observers consider this type to be true influenza in its pure form, and the frequency with which serious complications arise in the respiratory tract is responsible for its being grouped among the respiratory diseases

In the third type all the symptoms of the pure form are intensified and there comes about in addition early involvement of the parenchyma of the lung The pulmonary complication, if it may be considered such, manifests itself as a very serious hemorrhagic bronchopneumonia with an exceedingly high case fatality rate Many bacteriological studies of this kind of pneumonia have been made These bacteriological observations are of great interest in that they have demonstrated that the infecting organisms in the lung are not specific to the disease but consist of a considerable variety of microorganisms of different degrees of pathogenicity These organisms are in the order of their importance H influenzae, pneumococcus, S hemolyticus, S aureus, M catarrhalis and in certain rare instances, even such almost unheard of causative agents of pulmonary disease as meningococcus To many it seems unlikely that these various organisms can be the primary etiological agents of influenza but more likely that they fall in the class of secondary invaders that follow in the wake of some primary infectious agent

Some evidence has already been brought of the existence of such a primary etiological agent In the pandemic of influenza of 1918

Olitsky and Gates (2) isolated a filterable Gram negative anaerobic bacillus from the upper respiratory tract during the early hours of typical attacks of influenza This organism they called Bacterium pneumosintes or lung injurer, thus indicating the characteristic effect of influenzal infection In the 1918 epidemic, Yamanouchi, Sakukami and Iwushima and others (3) produced evidence to show that a filter passing organism may be the causative agent of influenza More recently Long, Bliss and Carpenter (4) have brought the most convincing proof yet obtained that influenza is caused by a true filterable virus Using filtered nasal washings from typical instances of influenza the latter investigators were able to induce in susceptible apes a disease closely resembling true influenza The material used was passed through fine porcelain candles and proven by the most careful methods to be free from visible cultivable bacteria As study of this disease progresses evidence seems to be accumulating that in influenza just as in the common cold, the sum of pathologic manifestations represents the cooperative activity of a varied group of microorganisms, perhaps with specificity characterizing the primary initiating agents, and heterogeneity the host of secondary organisms that participate in the infection

Just as individual instances of influenza manifest considerable variety in the sequence of events that is observed, so epidemics of this disease also show great variability of character I shall not attempt to describe the variations in detail but shall simply draw your attention to certain salient features Perhaps the most characteristic epidemic form in which influenza appears is that of the pandemic of world-wide distribution There have been many of these within the period of medical recording of disease and one may give a general description of such an outbreak in the following history In the beginning of the cycle there are numerous small outbreaks of moderate severity recurring in widely separated localities Within a short period of time, usually less than a year, the disease assumes a much more serious character, the proportion of typical attacks increases, pulmonary involvement becomes more conspicuous and the case fatality rate rises The disease then appears to pass rapidly from country to country until it may finally encircle the globe The exact point of origin of the severe disease is generally undeterminable, in fact, there

is some doubt concerning its even having a single point of origin In single countries, however, there does seem to be a progression of the epidemic in point of time from place to place After a variable period has elapsed the great wave of incidence begins to subside, only to be followed later by secondary waves of smaller proportion and lessened severity The interval between such pandemics is frequently a period of many years

In contrast to the pandemic form of influenza there exists another epidemic type which manifests itself over a limited geographical area, perhaps whole countries or at times in limited sections of a single country Individual attacks during this type of outbreak are likely to be less severe, to exhibit a greater variety of clinical manifestations, and symptoms of irritation of the respiratory tract are more prominent There have been in New York City since the great pandemic of influenza in 1918 a number of such minor outbreaks all of which have occurred at about the same time of year, the early winter months (5) Interestingly enough, this period coincides exactly with the major cyclic outbreak of the common cold which is, however, an annual occurrence At this time also, there may be a very widespread distribution of the pathogenic organisms of the respiratory tract and perhaps an enhanced virulence as well At the time of one such outbreak of so called influenza, we happened to be carrying out a survey of the incidence of H influenzae in the throats of normal individuals This rose from a low incidence of 40 per cent in the early fall to a high of 85 per cent in late December This peak of distribution of H influenzae in the normal population coincided exactly with the outbreak of epidemic influenza

It is of some interest that the type of pneumonia that was observed during the pandemic influenza of 1918 was predominantly bronchopneumonic in character In fact, some clinicians thought that during the period of the pandemic and for some time afterward there was a marked diminution of the incidence of typical lobar pneumonia This, I think, is in contrast to what is observed, at least in New York, during minor outbreaks of influenza for in my experience during such periods there is always a very marked increase in the number of instances of lobar pneumonia

Whether these two types of epidemics represent true influenza as

some epidemiologists think, or whether they are examples from an etiological standpoint of quite different diseases is impossible of decision, for up to the present time we have discovered no one characteristic by which we may say that a case or an epidemic is positively influenza However, I think there emerges quite clearly from these observations two possible explanations of the nature of these varying forms of epidemic influenza One is that there exists a specific virus of influenza which is present in all forms of the disease whether individual or epidemic and that variability of aspect is due to changes in virulence of the virus and variation in the character of the secondary organisms participating in the outbreak The other is that so-called epidemics of influenza are not uniform in nature but that some are due to a specific virus and others represent the coincidence of an epidemic outbreak of such an infection as the common cold with a period of widespread distribution and enhanced virulence of such common pathogenic organisms as H influenzae, pneumococcus and streptococcus Personally, I believe that in all probability both types of activity are concerned in the causation of that form of epidemic respiratory infection which goes under the name of epidemic influenza

There has recently been studied an animal disease, swine influenza, which seems to illustrate in a very significant manner the relationship of primary and secondary agents of infection of the respiratory tract These important investigations have been carried on by Shope and Lewis (6) in the Department of Animal Pathology of the Rockefeller Institute for Medical Research Swine influenza was first recognized as a clinical entity in 1918 at the time of the vast pandemic of human influenza Because of a certain marked resemblance in the symptoms of the two diseases investigators thought they might be the same and called the animal disease influenza

To quote Shope's description of the disease

> Swine influenza is essentially a disease of autumn and early winter and reaches epizootic proportions each year The onset is sudden and the incidence in an affected herd is practically 100 per cent Fever, anorexia, prostration of an extreme type, cough and a peculiar type of abdominal respiration are salient features of the disease The animals cry out when handled, which has been interpreted as evidence of muscular tenderness The period of illness is short, varying from two to eight days, and in uncom-

plicated cases the recovery is almost as sudden as the onset The mortality is stated to range from one to four per cent Fatal cases exhibit an extremely edematous type of broncho-pneumonia The principal features of the pathology of swine influenza are an exudative bronchitis, accompanied by marked damage of the bronchial epithelium and its cilia, a peribronchial round cell infiltration, and massive pulmonary atelectasis The latter is modified somewhat by a round cell infiltration of the alveolar walls The lymph nodes, especially the cervical and mediastinal ones, are hyperplastic and edematous There is usually a mild to moderate acute splenic tumor The mucosa of the stomach and colon is congested The pneumonia following swine influenza is characteristically lobular in type and of the same general distribution as the atelectasis The non-pneumonic areas of lung are extremely edematous and congested

Shope has been able to transmit this disease experimentally to healthy pigs by intranasal instillation of material from spontaneous cases occurring during natural outbreaks of the disease The experimental disease resembles very closely the epizootic form and can be easily communicated in series either by intranasal instillation or by pen contact The disease induced experimentally by material from three different epizootics was in general the same though there was some difference in severity and mortality

A number of attempts have been made to discover the causative microorganism of swine influenza and certain organisms have been isolated from the respiratory tracts of animals suffering from the disease The most significant observations of this nature are those of Lewis and Shope who obtained regularly from the respiratory tracts of swine experimentally infected a hemophilic bacillus This organism was also cultivated from spontaneous field cases of the disease but was never observed in the respiratory tracts of swine free from influenza The cultural and morphological characteristics of the organism are such as to justify its being called H influenzae (variety suis) It is non-pathogenic for certain laboratory animals and slightly pathogenic for others, and resembles exactly non indol producing strains of human H influenzae Of great interest is the fact that eleven out of thirteen attempts to induce symptoms of disease in swine by intranasal inoculations of pure cultures of H influenzae suis were entirely negative

Owing to the failure of this organism to produce the characteristic

disease, Shope searched for another etiological agent of the nature of the filterable viruses In the early experiments on the pathogenic properties of bacteria-free filtrates of infectious material from experimental instances of swine influenza it was possible to induce a definite but mild illness by the intranasal inoculation of such filtrates The disease thus induced was communicable to healthy animals and was transmitted by contact without alteration of its clinical or pathological characteristics It differed, however, from typical swine influenza in certain respects and appeared to be an incomplete form of the disease The constant presence of H influenzae in the typical examples of swine influenza suggested that the characteristics of the natural disease could be more exactly duplicated by infecting animals with mixtures containing both the filtrable agent and H influenzae When this was tried a disease typical of swine influenza in all clinical and pathological aspects and indistinguishable from that induced by unfiltered infectious material resulted in all instances Control animals receiving H influenzae alone developed no illness and those receiving the filterable agent alone developed the mild filtrate disease These experiments are interpreted as indicating that swine influenza is due to a filterable agent and H influenzae suis acting together It would seem that the virus is the communicable and primary agent and that its activities create a favorable medium for the entry and development of H influenzae which aggravates greatly the clinical and pathological manifestations of the disease The resemblance of this disease to certain forms of human influenza is obvious and it illustrates in a beautiful manner the very close and in this instance almost essential relationship which may exist between primary and secondary agents of infection in disease of the respiratory organs

Up to the present our discussion has been concerned mainly with what appear to be the most important types of primary infection of the respiratory tract, the common cold and influenza Associated in activity both in the individual and in the community with whatever are the etiological agents of these affections, are a considerable number of well known pathogenic microörganisms which are responsible for the concomitant and secondary pathologic processes The question may now be asked what significance have these primary infections of the respiratory tract in the sequence of events which leads to the develop-

ment of those most severe of all respiratory diseases, broncho- and lobar pneumonia A final elucidation of this problem must, of course, await the completed examination of the character and relationship of all the etiological agents concerned so that any consideration at the present time must of necessity be hypothetical The secondary nature of broncho-pneumonia both in association with the specific fevers and acute upper respiratory infection has long been appreciated by clinical observers Both in extreme youth and old age the development of broncho pneumonia is as a rule preceded by an attack of upper respiratory infection resembling very closely in its clinical manifestations the common cold As is well known broncho pneumonia is one of the very frequent complications of influenza and the variety of organisms concerned in its production suggests strongly that it is the result of secondary infection unless we assume a multiple bacterial etiology for influenza, a state of affairs that seems extremely unlikely I think it is fair to assume that most broncho pneumonia, excepting certain specific forms, is the secondary consequence of acute inflammation of the upper respiratory tract Whether the bacterial agent producing the pneumonia is identical with that causing the upper respiratory infection cannot be answered definitely as yet but it seems most likely that more than one agent is participating in some form of cooperative activity

The relationship of an attack of lobar pneumonia to an antecedent and predisposing acute upper respiratory infection is not quite so clear Lobar pneumonia appears superficially as an independent and primary disease of the lungs An individual in previous good health is suddenly seized with a pain in the side, a chill, an attack of vomiting, and shortly he experiences a high fever, delirium, extreme prostration and is in danger of losing his life When questioned he may recall no prodromal manifestations of any kind However, if careful inquiry is made both of the patient and members of his family, very frequently a history of acute upper respiratory infection resembling the common cold is obtained In a carefully conducted investigation of this kind we have been able to obtain the story of a premonitory upper respiratory infection in approximately seventy per cent of instances When in history taking attention is directed to this sequence of events, the frequent occurrence of a symptom complex resembling the ordinary

cold becomes a matter of common knowledge Here again, of course, the individuality of the agent responsible for the prodromal symptoms has not as yet been determined

In any consideration of the probable importance and significance of primary and secondary agents of infection of the respiratory organs, one must always bear in mind the following possibility There is great reason for believing that many examples of respiratory infection represent cooperative undertakings on the part of more than one micro-organism, a primary factor which prepares the way, and a secondary agent which takes advantage of the situation to effect its own peculiar type of injury At first the cooperative relationship of the two may be essential to the production of typical forms of the disease As a rule the more severe manifestations result from the activity of the secondary agent There is some reason for believing, however, that with frequent opportunity to produce disease and rapidity of transference from individual to individual, the secondary agent may develop enhanced infectiousness and therewith an independence of the helpful activity of the primary factor Thus it may become free to initiate disease on its own account

I shall now deal but a moment with certain diseases in which infection of the upper respiratory tract seems to be an important part of the pathologic process but in which the main morbid lesions are in organs not directly connected with the respiratory passages There are a number of such diseases and two of the most important are rheumatic fever (7) and glomerular nephritis In both of these conditions there is frequently an acute infection of the tonsils and throat with S hemolyticus This precedes by some days the onset of the typical clinical symptoms and hemolytic streptococcus may be not obtainable by throat culture at the time of appearance of specific phenomena Both of these diseases are likely to be characterized by frequent and severe recrudescences of the essential pathologic process Before such reappearance of activity there very frequently exists a respiratory infection which must be diagnosed clinically as the common cold This is especially true of exacerbations of the rheumatic process A recent statistical examination of patients admitted to the Presbyterian Hospital in New York for cardiac decompensation in rheumatic heart disease revealed that in 50 per cent of instances failure of the heart was

preceded by an upper respiratory infection resembling the common cold It is now of course well known that cardiac insufficiency in rheumatic disease is not merely the expression of mechanical disability but commonly results from a reactivation of the essential pathologic process The most satisfactory explanation of these events, we believe, is that the specific phenomena of these diseases are in the main the result of infection with hemolytic streptococcus Many sufferers, particularly from rheumatic disease, are chronic carriers of S hemolyticus, and with the acquisition of an acute upper respiratory infection of the type of the common cold the etiological agent of the latter disease may stimulate the streptococcus in question into renewed activity by creating circumstances that are favorable to its development A recrudescence of infection therefore occurs, toxic products are formed which pass into the blood stream and are widely distributed If the hypothesis concerning the possible specific relationship of S hemolyticus to certain types of rheumatic disease and nephritis be correct, and this belief is not new in the minds of investigators of these diseases, an explanation is offered of the frequent association of attacks of common cold with exacerbations of diseases of the heart and kidneys

You will recognize, of course, that much of the argument which I have presented rests upon hypothetical considerations and has for its purpose the presentation of the problem of respiratory infection and associated pathological conditions in such a manner as to indicate a possible pattern in which the relationships of cause and effect can be detected Were the essential facts known such an effort would be superfluous Many reliable observations have, however, been made, and their further exploitation particularly in reference to some reasonable conception of the problem of respiratory infection as a whole should make it possible to elucidate the complex interrelationships between microbic agents and pathological processes which are so conspicuous a feature of infectious disease of the respiratory organs

Perhaps a valuable generalization from the standpoint of the infecting microorganism would be, in the beginning, a separation of the causative agents into those of a primary and those of a secondary order That each of these agents is capable of inducing primary disease of the respiratory tract unassisted by the other seems not improbable As a rule, however, it would seem more commonly to

be the case that these microorganisms are mutually dependent upon cooperative effort in order to evolve the complex picture of respiratory infection Personally, I prefer to group them as primary agents, such as the etiological agents of the common cold and influenza and perhaps others, which initiate the pathologic process, and secondary invaders of the nature of the common pathogens of the respiratory tract that intensify and extend the harmful activity For a thorough understanding of the problem of acute respiratory disease the relationship both in time and character of activity of all the agents concerned is essential but at present it would seem to be most important to concentrate our efforts on an attempt to bring to light new knowledge concerning the nature and mode of action of the primary agents Tomorrow I shall describe for you certain experiments designed to assemble knowledge about what I believe to be one of these primary factors, the causative agent of the common cold

LECTURE II THE ETIOLOGY OF THE COMMON COLD

The effort to understand and interpret the natural history of any infectious disease confronts the investigator with problems of extraordinary complexity. The contemporary picture of such a disease is the consequence of a long series of episodes, and results from adaptation to environment of a number of interreacting agents each of which possesses to a high degree the capacity of intrinsic variation The epidemiology of an infectious disease concerns itself with the expression of the activity of such a disease within the community as a whole and is resolvable into the activities of the parasitic agent and the response of the species involved Etiology is more specifically concerned with the nature of the infecting microorganisms, and the pathology of the individual disease takes account of the variable responses of the animal host to the infection The relationship of such a complicated series of reactions is obviously impossible of resolution even in a limited outbreak of the simplest form of infection, and interpretation from an historical standpoint opposes to the imagination a barrier that is insurmountable It is wise, therefore, in considering an undertaking to comprehend the nature of an infectious disease, to approach the problem in a simple manner The most direct question that presents itself appears to be the identity of the causative or etiological agent

The question of the etiology of the common cold has now been recognized for many years as one of great importance and numerous efforts have been directed towards its solution That the disease is infectious in nature was suggested as early as 1873 by Huter shortly after the pathogenic significance of microorganisms was first recognized That a number of inflammatory reactions in the upper respiratory tract are due to agents other than bacteria is in all probability true For instance, there exists a group of cold-like disturbances that are of allergic origin and are caused by a variety of substances acting upon individuals who are specifically hypersensitive to these agents Furthermore, certain vasomotor reactions may simulate the common cold These types of disturbance may induce a certain amount of bacterial activity and may even closely resemble infections Apart from such conditions, however, there exist forms of upper respiratory disease, of which the common cold is the most frequent example, that in the opinion of most investigators are clearly infectious in origin They possess a definite epidemiology with clearly defined periods of increased seasonal incidence During such outbreaks a large proportion of individuals in the community are attacked and in limited groups such as schools and particularly the family, there appears to be a clear-cut transmission of the infectious agent from one individual to another In isolated communities a single infected individual coming in from the outside possesses the capacity of initiating an epidemic which sweeps with great rapidity throughout the entire population Individual attacks in any outbreak tend to be similar in character and the clinical manifestations of the disease are strongly suggestive of its infectious nature Whether there is a single agent which is responsible for all instances of the common cold or whether a variety of causative factors exist is not entirely clear at the present time

The problem of the investigation of the etiology of upper respiratory infection has from the early days been complicated by the recognition of the fact that normal individuals harbor in their respiratory tracts for longer or shorter periods of time potentially pathogenic organisms Important organisms belonging to this group are pneumococci, streptococci, staphylococci, H influenzae, certain Gram negative cocci, anaerobic bacilli and perhaps others of a pathogenic nature

served During the early stages there tended to be a quantitative diminution in the organisms obtained from the nasal secretions In the later stages such potentially pathogenic organisms as H influenzae and Streptococcus hemolyticus were present in the nose These organisms were practically never cultivated from the nose during health In the throat during colds, there was in general a shift in predominance from Gram negative cocci to the Gram positive non-hemolytic streptococci Various potentially pathogenic bacteria such as H influenzae, Staphylococcus aureus, and hemolytic streptococcus assumed increased prominence during the period of the cold These organisms were, however, frequently present in the throat secretions during the normal period, and the increased activity during colds usually occurred late in the disease and appeared as a secondary manifestation of the infection No organisms were found regularly in the cultures taken during the first days of the cold to which we felt a causative rôle could be assigned As a working hypothesis, therefore, we drew the conclusion that the symptoms of the common cold are not initiated by any of the common pathogens of the respiratory tract but that when these organisms appear during the disease they function as secondary agents in an inflammatory process causatively induced by some primary agent of unknown nature

Shortly after the great pandemic of influenza of 1918–19 Olitsky and Gates (10) and Olitsky and McCartney (11) described a previously unrecognized group of bacteria whose principal habitat is the upper respiratory tract These organisms are small Gram-negative anaerobic bacilli which in the form in which they exist in the nasopharyngeal secretions have the capacity to pass readily through Berkfeld V and N filters The most important member of this group the investigators named Bacterium pneumosintes, and because of its exclusive association with the early stages of epidemic influenza thought that it might be the etiological agent of this disease Later the above authors described similar organisms isolated both from normal individuals and those suffering from common colds The organisms were roughly grouped into different types on a basis of morphology, cultural characteristics, and serological reactions, and although their association with colds was interesting, no definite etiological rôle was assigned to them

In view of the association of such organisms with the common cold, we decided to submit them to a careful biological investigation in the hope of throwing light upon their relationship to colds As I have pointed out previously, familiarity with the bacterial flora of the upper respiratory ract in health is a prerequisite to correct interpretation of findings in the course of infection Accordingly, a group of healthy normals was followed for a period of several months to determine the presence of these filter passing anaerobes and during the same period search for the organisms was carried out in these subjects when they acquired colds In addition, numerous other individuals suffering from typical colds were also studied In addition, cultural and serological tests were made in order to discover if any particular type was more commonly found in individuals with colds than in healthy persons

The conclusions that we have arrived at from this study are that the organisms can be grouped, in general, morphologically and culturally according to the classification of Olitsky and Gates and Olitsky and McCartney There is a considerable range of variation within the individual groups and the organisms as a whole manifest a marked degree of heterogeneity They are nearly always present in the upper respiratory tract of healthy individuals but during attacks of common cold there appeared a striking decrease in incidence Variation in morphological and cultural characteristics is the rule and little if any serological inter-relationship is evident The organisms seem to be part of the harmless normal flora of the upper respiratory tract and their percentage of incidence (75 per cent) would probably rise higher if cultural methods were further improved No specific association of any one group with the common cold was noted and the observed reduction in incidence in colds makes improbable the assumption that they have a causal relationship to these infections

That the etiological agent of the common cold might be an ultra microscopic virus received impressive support from the experiments of Kruse (12) in 1914 This investigator was able to produce in human volunteers typical examples of colds by intranasal inoculation of fresh nasal secretions rendered bacteria-free by passage through a Berkfeld filter Kruse was apparently satisfied that the infectious agent of colds was a filterable virus and gave the organism a name

Following the studies of Kruse a number of other observers reported results of a similar character and Olitsky and McCartney (13) were even able to pass the agent, by means of filtered nasopharyngeal washings, from individual to individual in series producing in each instance infection typical of the common cold Other experiments were performed during this time in which the number of positive results obtained from the inoculation of human volunteers with filtrates from human colds were so few that in the opinion of the investigators the positive instances of infection might well be attributed to influences other than inoculated material such as accidental contact infection These findings raised some doubt concerning the validity of Kruse's hypothesis

We therefore determined to perform a similar series of experiments and moreover to carry them out in such a way that the influence of external and accidental factors in the production of infection might be minimized to the greatest possible degree We hoped, that should this undertaking develop results confirmatory of Kruse's view, a final conviction would be reached concerning the nature of the causative agent of the common cold

In the experimental study of human disease progress of the investigation is usually greatly facilitated when it is possible to transmit the infection to animals in reasonably typical form Susceptibility of suitable animals to certain varieties of human disease, unfortunately, is not common In searching about for an animal subject for experimentation with the common cold a number of species were considered Many animals are subject to respiratory infections that somewhat resemble colds but previous investigation of these animal diseases had indicated that they are in all probability due to microbic agents peculiar to the species in question

There was no sufficient reason for believing that the human infection would be communicable to these animals In pursuing the question further it was learned from Dr Francis G Blake, and later confirmed by interrogation of curators of zoological gardens, commercial animal dealers and others, that anthropoid apes experience respiratory infections very similar to the common cold in man Furthermore it was very soon discovered that all workers with the higher apes were unanimously of the opinion that these animals readily catch colds from human beings similarly afflicted

Having satisfied ourselves of the suitability of anthropoid apes for our purposes, we acquired a small colony of chimpanzees numbering from six to ten animals The apes ranged in age from two to four years and at the time of purchase had been in this country for from three months to over a year and as a consequence had experienced a variety of human contacts The cage rooms were maintained at constant temperature of 80°F and the animals were protected as carefully as possible against accidental infection from the outside

Very early in our study, we confirmed the truth of the reports regarding the susceptibility of anthropoids to human upper respiratory infection While our animal quarters were in course of construction the first two chimpanzees acquired by us, while boarding at a dealer's, both acquired colds from an infected keeper One of these animals developed bronchopneumonia from which he died and a number of organisms of human type, such as S hemolyticus, H influenzae and a Gram-negative anaerobic filter passer were recovered by culture from the lungs at autopsy Since that time we have had abundant opportunity to observe the readiness with which these animals acquire contact colds from human beings Such contact infection has been communicated to animals in the stock room in spite of the wearing of masks by keepers handling them, and such infection passes rapidly from animal to animal, usually involving the entire group During the past two years the rigor of our quarantine precautions has been relaxed somewhat and the chimpanzees have suffered from frequent spontaneous colds As I have mentioned before, there are during the year three major outbreaks of common cold among the population at large and it has been a matter of great interest to us that during the period of incidence of such outbreaks our stock of chimpanzees has in each instance suffered from an epidemic of colds usually involving 100 per cent of the animals under observation

In a chimpanzee the clinical picture of the common cold is much like that observed in a human child The following description is typical of a moderately severe attack At first there is a moderate amount of thin mucus in the nostrils By the end of the first day the animal appears sick and lassitude may be fairly striking The eyes are puffy and drooping, there is moderate to profuse nasal discharge of thick mucus which runs down over the upper lip, there is definite nasal

obstruction which makes it difficult for the animal to take liquid food and the breathing becomes audible There is occasional sneezing and cough The appetite is usually moderately impaired and rarely there has been diarrhoea Usually there is no elevation of temperature By the second day the nasal discharge becomes mucopurulent The throat has at times appeared inflamed By the fourth or fifth day the animal is usually much better and the discharge and nasal obstruction become much less Recovery is frequently complete within a week or ten days Occasionally there is a persistence of cough for several days resembling the bronchitis so frequently observed as a complication of human colds Not uncommonly there is a continuance of purulent nasal discharge for days or weeks suggesting a paranasal sinusitis This has been particularly true of one of the animals which has a large polypoid growth in the posterior nasopharynx

Our observations concerning the susceptibility and immunity of chimpanzees to cold have been of some interest Up to the present time all apes coming into our possession have been highly susceptible to the type of upper respiratory infection resembling the common cold The number of colds experienced year in and year out by each animal is roughly the same There appears to be little if any real immunity and the interval between successive infections ranges from one to three months The longest period of freedom from infection is the summer months between May and September With one exception, when the animals had a respiratory infection clinically resembling influenza, the colds experienced at different times of the year appear to be similar

Soon after acquiring the colony of chimpanzees a study was commenced to determine the bacterial flora of their noses and throats Swab cultures were made upon fresh rabbit's blood agar plates and the types of organisms present were noted

The bacteria of the throat are surprisingly similar in man and ape The usual basic organisms, non-hemolytic streptococci and Gram-negative cocci, are identical in incidence H influenzae and hemolytic streptococci are more frequently present in the ape than in man B coli appears in the ape as a result of the unhygienic habits of the animal Other differences are only of slight degree

In the nasal cultures, staphylococci which are usually the predominating organism in man, are the same in incidence in the chim-

panzee Diphtheroid bacilli very characteristic of the human nasal flora are rather lower in percentage incidence in the ape Streptobacilli seem to be peculiar to the animal and with the incidentally present B coli constitute the only qualitative bacterial difference The higher percentage in the noses of apes of certain organisms such as Gram-negative cocci, non-hemolytic streptococci, H influenzae, etc , which are usually regularly present in the throats of both man and ape are probably due to anatomical differences Gram-negative filter passing anaerobes have also been cultivated from the nasal washings of normal apes but careful study of the incidence and character of these organisms has not been attempted because of the difficulty of securing washings

These studies indicate that there is a very close resemblance biologically between the respiratory tracts of chimpanzees and man and that these apes would probably be a very suitable animal for the purpose of transmitting human colds experimentally by means of filtered naso-pharyngeal washings These animals were therefore chosen for inoculation with infectious material from human beings suffering from the common cold Whenever experimental procedures were in progress the chimpanzees were kept in specially organized rooms under rigid quarantine A foreperiod of from five days to two weeks was provided in order to test the efficiency of the isolation and to guard against the existence of possible latent respiratory infection At the conclusion of this period of preliminary observation, individuals suffering from suitable types of colds were sought out The type of cold selected was one of not more than twenty-four hours' duration A special effort was made to exclude upper respiratory infections that did not conform strictly to the classical clinical types, such, for example as the so called grippy varieties in which fever or marked constitutional symptoms were manifest Nasopharyngeal washings were obtained by running warmed buffered broth through the nostrils and out the mouth and then by gargling with a small amount of additional broth The material was quickly passed through Berkefeld or Seitz filters and the filtered material was further controlled for the presence of the virus of herpes labialis by the intracisternal inoculation of rabbits As soon as possible after filtration, usually less than one hour, the experimental animals were inoculated intranasally with

the filtrate and then carefully observed for the development of symptoms The very first animals so inoculated developed infection of the respiratory tract resembling the common cold There was usually an incubation period of from twenty-four to forty-eight hours after which time the characteristic symptoms began to manifest themselves These were always clearly objective in character and consisted of the appearance of increased mucus in the nose followed by profuse mucus or mucopurulent discharge, nasal obstruction and frequently sneezing or coughing Many times there was loss of appetite and occasionally diarrhoea The throat at times became inflamed but there was practically never a rise in temperature sufficient to be called a fever The signs of infection commonly lasted about a week but when secondary involvement of the paranasal sinuses or trachea and larger bronchi occurred cough and nasal discharge continued for a much longer period In other words, these experimental infections resembled in every detail the spontaneous colds observed in apes and bore a striking similarity to the same disease in man

These experimental colds could be passed from ape to ape by intranasal inoculation of filtered material from the infected animal The contagiousness of the experimental cold was proven by placing a contact healthy chimpanzee in the same cage with the experimentally infected animal under which conditions symptoms usually appeared in the healthy ape within forty-eight hours of the establishment of contact The early filtrates of nasopharyngeal washings from human beings contained in a large proportion of instances Gram-negative filter passing anaerobes of the type described by Olitsky and Gates Later by the use of the Seitz filter it was found possible to rid the filtrates of these organisms During the course of these experiments in all forty-four experimental inoculations of filtered infected human material into chimpanzees were made and of these twelve gave rise to experimental colds of typical character

While each animal was under observation during the course of an experiment, daily records were made of the character of the bacterial flora of the nose and throat Such observations were made frequently during the intervals so that we were at all times thoroughly familiar with the types of organisms present Perhaps one of the most significant occurrences in experimental infection of the ape has been the

apparent increase of activity on the part of the potential pathogens habitually present in the throat flora of the apes Coincident with the appearance of symptoms, pneumococcus, S hemolyticus and H influenzae have developed in greatly increased numbers and have spread over a wide area of the nasopharyngeal mucous membranes These organisms become during this time conspicuous even in the nose where they are seldom present under normal conditions We have also observed that during the period of acute infection animals who carry hemolytic streptococcus may communicate this organism to contact animals Such transference does not readily take place from carrier to contact in the absence of acute respiratory infection in the carrier animal

In order to control as far as possible the experimental inoculation of apes with human colds, these same animals were given filtered nasopharyngeal washings from healthy individuals In order to reduce the likelihood of including carriers of the active agent as sources of normal washings, the summer months were selected for this experiment, and the material was obtained from individuals who had no history of a cold for at least three to four months Following inoculation of filtered washings from these subjects no change in the health of the animals was observed No mucous discharge from the nose developed and no perceptible alteration of the nasopharyngeal bacterial flora occurred In short, no agent either bacterial or of other nature seemed to be present in normal human secretions which could induce in apes the symptoms of a common cold

As a consequence of the foregoing observations, and the harmless character of the experimental cold in the chimpanzee we considered it advisable to attempt the experimental transmission of the common cold from man to man For this purpose human volunteers, preferably young adults, were secured In order to meet the usual criticism directed against human transmission experiments that the subjects were continuously exposed to accidental contact infection, the volunteers were placed under a rigorous isolation of the type developed for apes, and under the control of a nurse experienced in the application of surgical aseptic technic On entering quarantine the subjects were given a thorough physical examination and all individuals considered likely to suffer from complications of any sort were excluded from the

test. A study of the candidates' throat bacteria was also made and only those accepted for the experiment whose respiratory tract was free from organisms that might be considered potentially capable of producing unpleasant complications The technic of preparation of the filtrates of nasopharyngeal washings from human beings with colds, and of inoculation of this material intranasally into volunteers was similar to that employed in chimpanzees In the early experiments the filtrates contained Gram-negative filter passing anaerobes but it was found possible later to remove these by use of the Seitz filter The results obtained in this study were in every way comparable to those observed in apes Of twenty-one such human transmission experiments performed, nine have given rise to typical cold-like infections in the inoculated subject These experimental colds have been readily passed from human being to human being in series Objective signs of upper respiratory infection were considered indispensable for the interpretation of a result as positive These consisted in affection of the mucous membranes of the eyes, profuse nasal discharge, inflammation of the naso-pharynx and cough

The incubation period of the experimental cold in man is twenty-four hours or less, somewhat shorter than in the chimpanzee The common symptoms are stuffiness of the nose, sneezing, sore throat, and headache No fever has been observed during the course of the attacks The duration of the experimental cold was approximately a week Occasionally complications developed such as paranasal sinusitis and mucopurulent tracheitis and bronchitis, which greatly prolonged the manifestations A few of the subjects experienced an increase in symptoms on being released from quarantine This in all probability indicated secondary infection resulting from exposure to outside contacts Secondary infection obviously could not take place during the period of isolation and furthermore, individuals harboring potentially dangerous organisms having been excluded from the tests less severe symptoms were to be expected than in an individual going about his daily affairs and being frequently exposed to secondary infection by many contacts with other people While these experiments on human volunteers were in progress, a parallel series of similar observations on human beings were carried out by Long and Doull (14) These observers obtained results in conformity with those

reported by the early investigators of the common cold and with our own and were of particular interest in that the human filtrates used were free from Gram-negative filter-passing anaerobes

The foregoing experiments lead us to certain definite conclusions The contagious cold in human beings is due to an invisible agent which passes readily through filters which hold back all ordinary bacteria and in all likelihood belongs to the group of so-called ultra microscopic viruses Colds can be transmitted from man to chimpanzee, from chimpanzee to chimpanzee, and from man to man by bacteria-free filtrates of nasopharyngeal washings obtained from individuals suffering from spontaneous colds These experimental colds resemble in all respects colds spontaneously contracted in the natural environment In apes one of the significant effects of infection with the filterable virus of the common cold is the stimulation into greatly increased activity of any pathogenic organism that may happen to be present in the upper respiratory tract at the time of development of the cold This we regard as of great importance since it serves to explain the marked secondary activity in the respiratory tract of such organisms as pneumococcus, streptococcus and H influenzae which lead to the severe complications which sometimes follow the common cold and influenza Though this influence is not so directly observable in human beings there is every reason to believe, as I have suggested in the previous lecture, that it is operative

In order to complete the proof that the common cold is caused by a filterable virus our next efforts were directed toward cultivating the causative agent in vitro and producing typical attacks of the disease with the cultivated virus The first steps in the successful carrying out of such a procedure were naturally directed toward an attempt to preserve the virus in an active form outside the animal body In order to test survival of the virus after removal from the human body nasopharyngeal washings were obtained from individuals within the first twenty-four hours of a typical attack of common cold The material was quickly passed through a Seitz filter, and the filtrate subsequently tested for its capacity to induce colds in chimpanzees and human voluntcers The filtrates with cystein hydrochloride added were preserved anaerobically under vaseline seal both at room and at ice-box temperature In some instances the filtrate was con-

centrated to approximately one-seventh its original volume by vacuum distillation Of twelve inoculations of filtrates preserved in this manner nine have produced in the inoculated subject a typical attack of the common cold The duration of time of preservation of activity in stored filtrates has ranged from four to thirteen days Tests of survival beyond the thirteenth day have not been made Positive results have been obtained with filtrates kept at room temperature and with those kept at ice-box temperature, and with both the unconcentrated filtrate and with that concentrated by vacuum distillation From these experiments we conclude that the virus of the common cold survives under suitable conditions for at least thirteen days after removal from the human body

Having determined the capacity of this virus to survive in what might be considered an adverse environment, an effort was next made to cultivate the agent in living tissue medium Foster (15) has previously reported the cultivation of an organism from patients suffering from the common cold, and the communication of colds to human volunteers with the early cultures of the agent The method of culture chosen by us has been that developed by Maitland and Maitland (16) and by Li and Rivers (17)

Ten day chick embryos are washed and suspended either in Tyrode's solution or in buffered bouillon prepared from the peptone of Dubos and to which 0 1 per cent gelatin has been added At all times an effort has been made to protect the agent against the deleterious action of peroxides by careful preservation of anaerobic conditions by the addition of cystein hydrochloride and the use of the vaseline seal The cultures were incubated at 37°C for from three to nine days, three- to four-day periods being the best

The material used for cultivation was obtained from an individual with a cold of more than moderate severity The washings were filtered through a Seitz filter and the infection was passed in series through three human volunteers The last individual inoculated developed a cold of unusual severity perhaps indicating an accession of virulence by the virus Nasopharyngeal washings were obtained from this subject, filtered through a Seitz filter, concentrated sevenfold by vacuum distillation, and preserved for five days at ice-box temperature After the lapse of this interval, 0 25 cc of the concen-

trated material was inoculated into tissue medium of the nature described The culture was incubated for five days at 37°C At the end of this time a human volunteer was inoculated and within the usual incubation period developed a cold with symptoms of rather a mild character

From this time on the virus was carried in tissue medium, and transferred after periods of from three to nine days At intervals cultures were chosen for the inoculation of experimental subjects, under the customary isolation Positive inoculations were obtained with third, sixth, tenth, twelfth, fifteenth and twenty-fifth generations From the tenth generation on it was considered that the original material inoculated had been diluted practically to the point of disappearance The fifteenth generation representing a dilution of the inoculum of approximately 1 2 quadrillion was inoculated into three human volunteers Of these two developed colds of unusually severe symptoms, complete nasal obstruction, frontal headache, malaise, loss of appetite, nasal discharge, and pronounced cough Both had complications, one a purulent sinusitis requiring surgical intervention and the other a mucopurulent tracheo-bronchitis These two culture colds were successfully passed in series to two additional volunteers

This culture of cold virus was carried in tissue medium in an active state for 106 days No tests subsequent to this period have been made In addition to the cultures described two other cultures have been made and tested One of these gave a positive result in the seventeenth generation and the other in the nineteenth and fifty-first generation [1] In all, twenty-three human volunteers have been inoculated with the culture virus and of these thirteen, or fifty-seven per cent, have developed colds within the usual incubation period Of eight chimpanzees inoculated with culture virus, two have developed positive infections but with prolonged incubation periods These animals appear to be not as susceptible to the cultivated virus as do human beings Control inoculation of the constituents of the medium, of the tissue medium itself and of heated tissue culture virus have failed to produce progressive infection though at times signs of temporary irritation have appeared

[1] Up to the present, five strains of filterable virus from acute upper respiratory infections in human beings have been cultivated by us One of these is more than a year old and active after eighty three generations

Powell and Clowes (18) have recently confirmed the cultivation of the virus of common cold in tissue medium These observers inoculated human volunteers intranasally with different generations of culture virus and obtained positive results in twenty-two out of thirty-two inoculations performed, an incidence of infection of 69 per cent Isolation was not practiced but the experiments were conducted during a period of low cold incidence, 8 75 per cent in the control group This culture maintained its full virulence in the twenty-seventh generation over a period of seven months At last reports the culture was still active

To review briefly, the common types of acute infection of the respiratory tract, both in the individual and the community at large, represent cooperative undertakings on the part of groups of microorganisms These groups of organisms can most profitably be considered to function as primary and secondary agents of infection For the complete understanding of respiratory infection the interrelationship of activity between the two orders of infectious organisms must be worked out It seems likely that the two most important types of primary acute respiratory infection are represented by the common cold and influenza The etiological agent of the first of these has been proven to be a filterable virus a part of whose action seems to be the promotion of secondary bacterial infection Suggestive facts of a similar character have already been brought to light in the study of influenza The number of biological types of such primary infective agents of the respiratory tract remains for the future to decide

The experimental work presented in these lectures represents a cooperative investigation on the part of myself and my collaborators, Gerald S Shibley, Franklin M Hanger, Katherine C Mills, and Yale Kneeland, Jr (19)

BIBLIOGRAPHY[3]

(1) Kneeland, Yale, Jr, and Dawes, Carolina, F Jour Exp Med, 1932, 55, 735

(2) Olitsky, P K, and Gates, F L Jour Exp Med, 1921, 33, 713

[3] For a complete bibliography of the subjects discussed in these lectures the reader is referred to The Common Cold, David Thomson and Robert Thomson, Annals of the Pickett-Thomson Research Laboratory, 1932, Vol VIII

(3) Dujarric de la Riviere, M R Comp Acad des Sci, 1918, 167, 606
Selter, H Deut Med Woch, 1918, 44, 932
Nicolle, C and Lebailly C Ann de l'Inst Past 1919, 33, 395
Yamanouchi, Sakakami and Iwushima Lancet, 1919, Vol I, 971
(4) Long, P H, Bliss, E A, and Carpenter, H M J A M A, 1931, 97, 1122
(5) Bull Dept of Health, City of New York, 1931, 20, 17
(6) Shope, R E Jour Exp Med, 1931, 54, 349
Lewis, P A, and Shope, R E Ibid, 1931, 54, 361
Shope, R E Ibid, 1931, 54, 373
(7) Coburn, A F The Factor of Infection in the Rheumatic State, Williams & Wilkins, Baltimore, 1931
(8) Kneeland, Yale, Jr Jour Exp Med, 1930, 51, 617
(9) Bloomfield, A L Bull Johns Hopkins Hosp, 1921, 32, 121
(10) Olitsky, P K, and Gates, F L Jour Exp Med, 1922, 36, 501
(11) Olitsky, P K, and McCartney, J E Jour Exp Med, 1923, 38, 427
(12) Kruse, W Munich Med Woch, 1914, 61, 1457
(13) Olitsky, P K, and McCartney, J E Loc cit
(14) Long, P H, and Doull, J A Proc Soc Exp Biol and Med, 1930, 28, 53
Long, P H, Doull, J A, Bourn, J M, and McComb, E Jour Exp Med, 1931, 53, 447
Long, P H, Bliss, C A, Carpenter, H N J A M A, 1931, 97, 1122
(15) Foster, G B, Jr Jour Am Med Assoc, 1916, 66, 1180
Foster, G B, Jr Jour Infect Dis, 1917, 21, 451
(16) Maitland, H B, and Maitland, M C Lancet, 1928, 2, 596
(17) Li, C P, and Rivers, T M Jour Exp Med, 1930, 52, 465
(18) Powell, H M, and Clowes, G H A Proc Soc Exp Biol and Med, 1931, 29, 332
(19) Shibley, G S, Hanger, F M, and Dochez, A R Jour Exp Med, 1926, 43, 415
Mills, K C, Shibley, G S, and Dochez, A R Jour Exp Med, 1928, 47, 193
Shibley, G S, Mills, K C, and Dochez, A R Proc Soc Exp Biol and Med, 1929, 27, 59
Dochez, A R, Shibley, G S, and Mills, K C Jour Exp Med, 1930, 52, 701
Shibley, G S, Mills, K C, and Dochez, A R Jour Am Med Assoc, 1930, 95, 1553
Dochez, A R, Mills, K C, Kneeland, Y, Jr Proc Soc Exp Biol and Med, 1931, 28, 513 1931, 29, 64
Dochez, A R, Mills, K C, Kneeland, Y, Jr Lancet, 1931, 547

CONTRIBUTIONS OF CHEMISTRY TO THE KNOWLEDGE OF IMMUNE PROCESSES[1]

MICHAEL HEIDELBERGER, PH D

From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York City

Eight years have elapsed since a Harvey Lecture has dealt primarily with the chemical basis of immunology In that period chemistry has done much to systematize and clarify the knowledge of the complex processes resulting in resistance or immunity to disease Several leaders in this recent progress are in the audience tonight, and I should have preferred to be a listener, drawing fresh inspiration from their experience and vision However, I shall do the best I can

I should like first to recall some of the chemical studies which have led to a clearer understanding of the concept "*Antigen*," then to make a like examination of the concept "*Antibody*," and finally to discuss such chemical knowledge as is available of antigen-antibody interactions

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amine which determines the specificity of the resulting compound antigen and may be termed the "hapten," for whether the protein be derived from the horse or the chicken the specificity of the new azo protein is the same Thus aniline azo horse serum (fig 1, formula *a*) stimulates the production of antibodies in the rabbit which react with

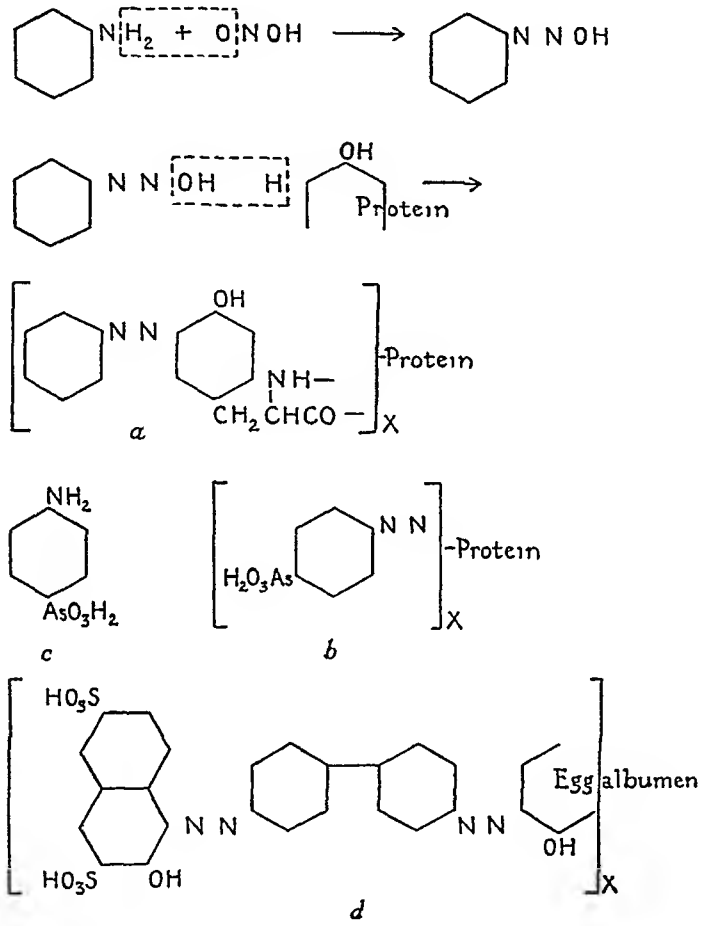

FIG 1

aniline azo chicken serum, although native horse serum and chicken serum are each species specific and the antisera to them do not cross-react Since the hapten introduced enters and modifies the tyrosine groupings and perhaps other cyclic groups of the protein, it would appear that these amino acids—chiefly tyrosine and histidine—play an

important rôle in the specificity of antigens, and when altered by the introduction of other substances, permit the establishment of a new specificity characteristic of the entering group, or hapten Alteration of other acidic or basic groups by acylation or methylation also changes the specificity, so that the tyrosine and histidine groups are not necessarily the only groups concerned

Up to this point it had seemed that of the naturally occurring classes of substances only the proteins possessed immunological reactivity In 1917 Dochez and Avery had found that culture filtrates of virulent pneumococci contained a "soluble specific substance" which was rigorously type specific, giving a precipitate with antiserum to the homologous pneumococcus type Zinsser and

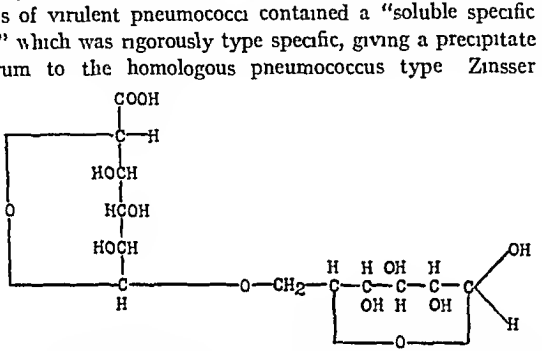

Fig 2 Aldobionic Acid from Type III Pneumococcus Specific Polysaccharide
Position of attachment of glucuronic acid to glucose is unknown

Parker found similar reactive products in extracts of various microorganisms and called them "residue antigens" A study of the "soluble specific substances" of type II and type III pneumococcus by Avery and myself showed that each was a chemically distinct, nitrogen-free polysaccharide and thus established the participation of the sugars in immune reactions and in the determination of bacterial specificity Indeed, when one considers the enormous number of polysaccharides possible on account of the many known sugars and the multiplicity of arrangements and isomeric forms in which they may be built up into polysaccharides—a multiplicity and variety approached only by the proteins—it does not appear strange that the polymeric sugars should often have immunological properties Sub-

sequent work with Goebel showed the presence of nitrogenous sugars in the type I pneumococcus specific polysaccharide and demonstrated that the type III specific sugar was built up of aldobionic acid units (fig 2)—the first discovery of a type of sugar acid which has since been found in other bacterial polysaccharides and even widely distributed in nature in the plant gums, such as gum arabic, and in the hemicelluloses In table 1 is given a summary of the properties of the specific polysaccharides of types I, II, III, and IV pneumococcus. It would now seem that nearly every species of bacterium is possessed of one or more specifically reactive polysaccharides, and although the connection of these sugars with microbic structure and virulence

TABLE 1

Comparison of specific polysaccharides of types I, II, III and IV pneumococcus

POLYSACCHARIDE	$[\alpha]_D$	ACID EQUIVALENT	TOTAL N	AMINO N	ACETYL N	HYDROLYSIS PRODUCTS	
			per cent	*per cent*	*per cent*	*calculated as glucose, per cent*	
Type I	+300°	310	5 0	2 5	0	28	(Galacturonic acid)
							(Amino sugar derivative)
Type II	+74°	1,250	0 0			70	Glucose
Type III	−33°	340	0 0			75	Aldobionic acid, glucose
Type IV	+30°	1,550	5 5	0 1	5 8	71	(Amino sugar derivative)
							Acetic acid

is not always as clear as in the case of Pneumococcus, they play a definite and often determining rôle in bacterial specificity While the specific carbohydrates may be classed as haptens, they represent a distinctive group which not only combines with antibody but precipitates it as well This property may be a function of their molecular weight, which Kendall and I have shown to be low in comparison with the common proteins, but high enough to be in close agreement with values only recently established by Haworth for glycogen and starch, namely 2400 to 6000 We have also found that partial hydrolysis products of specific polysaccharides of as low molecular weight as 500 still retain the power to precipitate antibody

I cannot tonight go into the brilliant synthesis of carbohydrate proteins and the reconstitution of the type III pneumococcus by Avery and Goebel, and the discovery by Avery and Dubos of an enzyme which strips the type III pneumococcus of its specific carbohydrate and its virulence This you will hear, I trust, in due course from Dr Avery

Another group of natural substances which may perhaps be classed as haptens are the lipoids, although it is beginning to appear as if the specificity formerly attributed to supposed lipoids such as the group of Forssman antigens and blood group specific substances may actually be due to specific polysaccharides In this connection it is interesting to recall the intimate relation between carbohydrate and lipoid in the horse-kidney Forssman antigen purified by Landsteiner and Levene, and the polysaccharides encountered by Anderson among the lipoid fractions of the tubercle bacillus While there is some evidence that highly specific antibodies may be developed in a very small percentage of animals following the injection of chemically pure members of the cholesterol group in admixture with pig serum, there is also evidence for and against the forcing of pure lecithin into antigenic combination We must, therefore, leave the subject of the immunological properties of lipoids in its present equivocal state

Now what can we, as chemists, say of the concept "*antibody*"? In his chapter in "A System of Bacteriology in Relation to Medicine," published in 1931, the English immunologist Dean wrote "we have no conclusive evidence that antibodies, in the sense of definite chemical substances, exist" This, I think, is an unnecessarily pessimistic view of existing data, for there is now much evidence that antibodies are actually modified serum globulins The chief uncertainty is caused by the insistence of certain immunologists that they have obtained protein-free antibody solutions These workers have forgotten the oft-repeated demonstration that tests for protein with chemical reagents fail at dilutions at which biological reactions such as anaphylaxis and bacterial agglutination readily occur, so that until such experiments result in the isolation of weighable amounts of protein-free antibody they can carry little conviction

On the other hand there is much that points toward the actual protein nature of antibodies Felton has shown that the protective

antibodies in antipneumococcus horse serum are more or less completely precipitated when the serum is added to twenty volumes of slightly acidulated water About 90 per cent of the serum proteins remain in solution and 60 to 80 per cent of the pneumococcus antibodies are concentrated in the precipitate and may be redissolved in saline and subjected to further purification By removal of an inactive fraction with acid and treatment with zinc or aluminium salts Felton claims to have obtained metal antibody compounds which are completely precipitable by the pneumococcus polysaccharide of the homologous type Unfortunately, the globulin solutions left after removal of the zinc or aluminium are specifically precipitable to the extent of only about 80 per cent Although absolutely pure antibody has not yet been isolated, Felton is evidently very close to the goal, and it should soon be possible to obtain antibody in sufficient quantity to study its differences from normal serum globulin

In addition to the preparation of nearly pure antibody there is now a mass of quantitative data supporting the protein nature of antibodies I shall mention here only the work of Marrack and Smith, showing that diphtheria toxin-antitoxin floccules consist mainly of denatured pseudoglobulin—the serum protein fraction with which antitoxin is commonly associated in the horse—and that the amount precipitated is independent of other serum proteins present or added

If antibody is actually modified serum globulin, how is it formed and what is its relation to the antigen? Buchner accounted for the specificity of antibody by the assumption that antigen or antigen fragments actually entered into the antibody complex Ehrlich abandoned this idea because of the large excess of antibody often produced Recent evidence against Buchner's hypothesis is, moreover, almost overwhelming Completing experiments begun by Doerr and Friedli, Berger and Erlenmeyer obtained highly potent antisera to atoxyl azo protein (fig 1, formula *b*) In this arsanilic acid (fig 1, formula *c*) is the hapten, or specificity determining portion, so that if the specificity of the resulting antibody depended on the incorporation of specific antigen fragments into the antibody molecule these fragments would necessarily contain arsenic, and it should be possible to detect arsenic in the antibody However, as much as 30 cc of antiserum contained no more than the faint traces of arsenic in

the same amount of normal serum The same experiment was made by Hooker and Boyd, again with a negative result Similarly, Kendall and I showed that the antibody to a deep red azo protein, R-salt-azo-benzidine-azo-crystalline egg albumen (fig 1, formula *d*), was not red, as was the corresponding hapten, but colorless Moreover, the quantitative work discussed later shows that the actual amount of antibody formed with the aid of minimal amounts of antigen is so great as practically to preclude the participation of specific antigen fragments in the antibody How, then, can antibodies be explained?

To the chemist, Breinl and Haurowitz' theory seems reasonable, although as yet without direct supporting evidence In their opinion, antigen or its partial degradation products may reach the points at which globulin synthesis is taking place in the animal body In the presence of this foreign protein or its products globulin synthesis is somewhat distorted, and distorted in a way characteristic for the foreign material, so that when the finished globulin encounters the foreign protein once more in the circulation or *in vitro*, interaction is possible A very clear presentation of this theory has been put forward independently by Mudd, and a similar view has been expressed by Alexander

Now that we have acquired a certain chemical perspective on antigens and antibodies, although many fundamental questions as to both are still unanswered, let us consider the mechanism of their interaction

Since most of the substances involved in immune reactions are presumably colloids, the simplest way of disposing of such phenomena as specific precipitation, agglutination, complement fixation or hemolysis, or toxin-antitoxin neutralization is to assume that oppositely charged colloidal particles combine to produce the observed effect This view was first upheld by Bordet, who later modified it in the sense that the immune reactions represented adsorption phenomena Ehrlich, on the other hand, insisted that actual chemical combination in definite proportions took place between antigen and antibody, and in this he was supported by Arrhenius and Madsen

While the colloidal theory offers a possible explanation of the course of events in an immune reaction, it fails entirely to account for the specificity of the reaction, as I trust the following experiment will show

I have here flasks of diluted type I and type III antipneumococcus sera To the type I antiserum I shall add a 1 10,000 solution of the specific polysaccharide of type III pneumococcus, and to the type III antiserum an equal amount of the type I specific polysaccharide The sera, of course, remain clear Let us recall that both flasks contain antibody globulin, presumably as the ionized sodium chloride compound, and on the alkaline side of the isoelectric point Charges on the antibody particles are therefore the same in both cases As for the specific polysaccharides, both are salts of polyvalent, complex sugar acids, so that the charges on the particles of both must be of much the same order If the immune reaction depended, then, on particle charges there should again be no evidence of change when I take some of the equally charged particles from each flask and add them to the other But type I polysaccharide has thus been added to type I serum, and type III polysaccharide to type III serum, specific precipitation occurs, and the conclusion seems inescapable that the specific interaction is a chemical union To draw a simple analogy from inorganic chemistry, there will, of course, be no precipitate when I add sodium acetate to barium chloride, but if I add sodium sulfate, specific precipitation of barium sulfate occurs at once

Of all the immune reactions the precipitin reaction is the simplest, but owing to analytical chemical difficulties it has only recently been possible to subject the reaction to strict quantitative study The analytical problem can be considerably simplified by the use of the type III pneumococcus specific polysaccharide, which is a nitrogen-free substance of such definite properties as to suggest that it is in a state of high purity Type III pneumococcus antibody may be readily obtained by the Felton method, and while not pure, contains 40 to 50 per cent of specifically precipitable protein If one admits that antibody is protein, it should be possible, by adding known amounts of nitrogen-free polysaccharide to measured amounts of antibody solution, to determine by means of nitrogen analyses the amount of antibody precipitated Kendall and I have been engaged in such studies for several years, and while the work is not completed a few conclusions seem possible and several practical results have been attained

If a very small amount of type III pneumococcus polysaccharide,

which we shall call S, is added to a relatively large amount of antibody, which we shall call A, it is found that as much as 180 mgm of antibody may be precipitated for each milligram of S As increasing amounts of S are added in proportion to the amount of A this ratio decreases, but all of the S added is precipitated, leaving antibody in excess Finally, with increasing amounts of S, a point is reached at which there occurs for the first time a very slight excess of S At this point there is also a small amount of antibody remaining in solution This stage we have called the "equivalence point," and at this point the ratio of S to A is approximately 1 60 If the amount of S is now further increased the traces of A in solution are first precipitated, but with relatively large amounts of S, the precipitate formed becomes less and less, until with higher concentrations of S no precipitation takes place The colloid chemist would say that the precipitate is "peptized" by the excess of S, but we have confirmed Arrhenius' belief in a soluble compound and shown that in this inhibition zone new, more soluble compounds are formed in which the most soluble contains one more molecule of S than the less soluble phase The findings may be schematized by the following equations

$$S + 3A \rightleftharpoons \underline{SA_3}$$

$$\underline{SA_3} + 2S \rightleftharpoons 3\underline{SA}$$

$$\underline{SA} + (x - 1)S \rightleftharpoons S_xA$$

in which SA_3 represents the limiting compound formed in the region of excess antibody, SA the composition of the precipitate at the "equivalence point," and S_xA the composition of the most soluble material in the inhibition zone Each equation can be shown to represent a reversible equilibrium, and since the antibody sodium chloride complex is ionized and S is the salt of a highly ionized polyvalent acid, the equilibria appear to be ionic and the application of the mass law seems justified The precipitin reaction between S and its homologous antibody is thus no different in principle from an inorganic precipitation such as the specific reaction we have seen between barium and sulfate ions Nor does one have to search far for at least a partial analogy to the inhibition zone if we recall that the insoluble

silver cyanide is soluble in an excess of potassium cyanide solution The equations are

$$Ba^{++} + SO_4^{=} \rightleftharpoons \underline{BaSO_4}$$

and

$$Ag^{+} + CN^{-} \rightleftharpoons \underline{AgCN}, \quad \underline{AgCN} + CN^{-} \rightleftharpoons Ag(CN)_2^{-}$$

Thus one need not be limited as by the colloid theory to names such as adsorption, hydrophilic, hydrophobic, or peptization, which are descriptive but difficult to translate into quantitative terms Nor need one be limited to the analogy of the union of a weak acid with a weak base, which formed the point of departure of Arrhenius' formulation of immune reactions, for the multivalence of A and S with respect to each other is emphasized and quantitatively accounted for The failure of the older theory of antigen-antibody union to do this was pointed out many years ago by Fleischmann and Michaelis

Several immunological puzzles of long standing may be accounted for by treatment of the precipitin reaction in this fashion according to the laws of classical chemistry Take, for example, the difficulty of explaining the coexistence of antigen and antibody in the body fluids At the equivalence point, at which the equilibrium may be represented by

$$\frac{[S]\,[A]}{[SA]} = K$$

free A and free S are in equilibrium with the insoluble compound SA, and either is precipitated on the addition of a small amount of the other, just as addition of either ion to a saturated solution of a sparingly soluble salt produces a fresh precipitate According to this view, the amount of A and S in solution should depend upon the equilibrium constant and would vary with every system studied Thus in the egg albumen-antibody reaction Culbertson reported that the amounts of antigen and antibody at the equivalence point were too small to detect Breinl and Haurowitz, on the other hand, studying the hemoglobin-antibody reaction, found such large amounts of both in equilibrium with the precipitate that they were unable to interpret their results However, by using a dissociation constant deducible

from their data, we have been able to account satisfactorily for their findings

Another immunological puzzle which can now be explained is the Danysz phenomenon, and one may even predict for any given antibody solution how much antigen will be left over if the amount necessary to reach the equivalence point is added in definite fractions instead of all at once A glance at figure 3 will make this clear The curve shows the amount of antibody precipitated from an antibody solution by

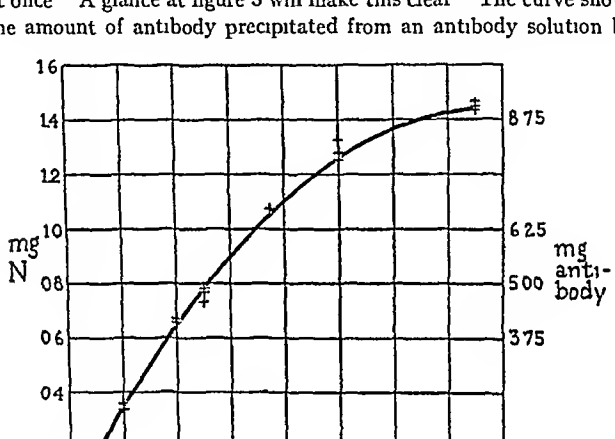

FIG 3

varying amounts of S At the right is the equivalence point, at which S just begins to show in slight excess S, 0 15 mgm , and 9 0 mgm of antibody are thus equivalent if the S is added at one time Let us, however, first add one-half of the amount of S, or 0 075 mgm Under these conditions antibody is in relative excess, and as we have seen in our previous study, the precipitate will not have the composition SA, but will be somewhere in the range SA_3-SA From the graph, the actual amount of antibody precipitated is seen to be 6 7 mgm But

this is three-quarters of the antibody precipitated by the entire amount of S when added at once, and we still have one-half of the S left over This will, of course, be far more than necessary to reach the equivalence point, and the excess can easily be calculated We have, then, given a simple, quantitative interpretation of the Danysz phenomenon in terms of the laws of classical chemistry, whereas it is often cited in illustration of the colloidal or adsorptive nature of immune reactions Indeed, the reaction cannot in this case be one of adsorption, for if the fractional amount of S distributed itself over the surface of the antibody, removal of the precipitate would remove all the antibody But we have seen that a definite and predictable portion of antibody is left over, and in order to precipitate this from the supernatant a new and definite amount of S must be added

The method illustrated in figure 3 is also of interest in another connection, since it provides a means for the quantitative micro-determination of any specific polysaccharide or antigen which can be obtained in a state of purity All that is necessary is to calibrate an antibody solution or serum with known amounts of polysaccharide or antigen, taking care always to have an excess of antibody, so that all of the polysaccharide or antigen will be precipitated Nitrogen is then determined in the washed precipitate by the micro-Kjeldahl method and a curve is constructed from the antibody precipitated, deducting the amount of nitrogen in the precipitate due to the polysaccharide, if this contains nitrogen, or to the antigen Amounts of specific polysaccharide as low as 0 01 mgm may be determined in this way with a fair degree of accuracy, since the amount of antibody precipitated is many times that of the hapten or antigen in combination

But it is not only the antigen or hapten for which a quantitative analysis may now be made The antibody titer of a serum has usually been given in terms of the highest dilution at which it will agglutinate, hemolyze, or precipitate the antigen, in terms of the volume of toxin it will neutralize, in terms of mouse protection,—all relative and often inaccurate measures giving no idea whatsoever of the actual mass of antibody involved If, however, it is admitted that antibodies are proteins, an absolute determination of antibody is now possible

Returning to the last equation, let us recall that at the equivalence

point the specific precipitate SA is in equilibrium with small amounts of A and S (see p 288) Clearly in order to obtain the maximum amount of specifically precipitable antibody it is necessary to add a somewhat greater amount of S, so that the excess will combine with and precipitate as much as possible of the small amount of A remaining in solution The conditions are thus established for the precipitation from any serum of the maximum amount of specifically precipitable antibody, and we have made this the basis of a quantitative method for the determination of antibody The method consists in the addition of a *slight* excess of specific polysaccharide or antigen to an immune serum or antibody solution and an analysis of the washed precipitate by the micro-Kjeldahl method for nitrogen Deduction of the amount of nitrogen due to the hapten or antigen and multiplication by the factor for protein gives milligrams of specifically precipitable antibody for the volume of serum taken This may be as little as 0 5 cc in the case of potent sera The micro-Kjeldahl method had previously been used by Wu for the analysis of specific precipitates, but the conditions for the maximum precipitation of antibody were not at that time understood

The first application of this method was in an attempt to determine whether or not mouse protection and specific precipitation ran parallel in type I antipneumococcus horse sera Eleven sera were studied and it was found that they contained amounts of specifically precipitable protein ranging from 0 7 to 9 7 mgm per cubic centimeter Parallel mouse protection tests made by Sia ranged from 50 to 1600 units When the sera were arranged in the order of increasing mouse protection it was found that they were also in the order of increasing amounts of specifically precipitable antibody per cubic centimeter Seven milligrams per cubic centimeter corresponded roughly to 1000 mouse protective units Working with a very much larger number of sera, Felton then confirmed the high degree of correlation between mouse protection and the maximum amount of specifically precipitable protein, so that at least in the case of type I antipneumococcus sera it would seem reasonable to substitute the analytical method for the time-consuming, expensive and difficult mouse protection test

The next application of the method was in the quantitative study of an antigen-antibody system In this case, since antigen and antibody

are both considered proteins, it became necessary to distinguish between antigen nitrogen and antibody nitrogen in the specific precipitate This had already been accomplished in brief studies by Wu, who determined hemoglobin and total nitrogen in the hemoglobin-antibody precipitate, and also analyzed iodoalbumin-antibody precipitates for iodine and nitrogen The simplest method, however, seemed to us to be the colorimetric determination of the amount of an azo protein precipitated by its homologous antibody. For this purpose the yellow azo proteins such as those previously discussed seemed too light in shade, and accordingly the R-salt-azo-benzidine-azo-crystalline egg albumen derivative was made of which you have already seen the formula As you see, this is an intense red, and may be quantitatively determined by its color in dilutions even greater than 1 100,000 The specific precipitate with its homologous antibody varies from pink to deep red, depending on the relative proportions of the reactants, and each component may be determined separately in the precipitate or in the supernatant, the antigen by comparison with a standard solution, and the antibody as previously described In this way it has been possible to show that antigen and antibody in this system, too, are multivalent with respect to each other—that is, that the composition of the precipitate varies according to the relative proportions of the reactants Thus the precipitin reaction between a complete antigen and its homologous antibody proceeds in the same manner as that between a specific polysaccharide and its antibody, the differences being solely numerical

With the aid of the quantitative method, it is possible to follow antibody production in its various stages in animals, and such a study is in course of publication One thing which it has brought out clearly is the astounding disproportion between the amount of antigen injected and the amount of antibody produced in the animal While this has long been realized in a qualitative way, we have found that the serum of reactive rabbits may contain as much as 80 to 110 mgm of precipitin per milligram of antigen injected Since there is antibody in the tissues as well, this may be taken as supplementing the other evidence quoted against the actual entrance of specific antigen fragments into the antibody molecule

Culbertson has also used the quantitative method in a study of the

egg albumen-antibody system and has developed a simple modification applicable to that system With its aid he has shown that the circulating antibody alone accounts quantitatively for the rapid disappearance of egg albumen injected into the circulation of immunized rabbits, and he has also used the method for the determination of blood volume in rabbits

It is thus evident that a simple, quantitative treatment of the precipitin reaction according to the laws of classical chemistry yields information as to the nature of this immune reaction, affords an explanation for several puzzling phenomena, provides a means for studying the formation of antibodies, and should have practical value in the standardization of immune sera and as a tool in immunological research Kendall and I have been working toward a complete and quantitative theory of the precipitin reaction, but there are still difficulties in the way of its realization Undoubtedly other explanations of the reaction are possible, but the ones based upon colloidal chemistry and adsorptive processes have failed to go beyond the qualitative stage and have been sterile in their application

How far a treatment similar to that we have given the precipitin reaction may be used for other immune reactions remains largely to be seen True, Francis has shown an extensive parallel between the successive stages of the precipitin reaction and the agglutination of type specific pneumococci, so that bacterial agglutination, as foreshadowed by the work of Northrop and de Kruif, Shibley, and others, is merely a precipitin reaction at the surface of bacteria, and, subject to this restriction, is governed by the same laws

The toxin-antitoxin reaction, involving as it does the direct union of antigen and antibody, is very similar to the precipitin reaction and is, indeed, often accompanied by flocculation That the precipitate is derived mainly from the serum pseudoglobulin was shown by Marrack and Smith, as previously mentioned The chief difficulties in the way of a chemical study of the reaction lie in the lack of chemical knowledge of toxins, for pure toxin has never been isolated, and in the cumbersome mechanism of the animal tests for toxin and antitoxin The use of the flocculation reaction for the measurement in relative terms of either component now seems feasible, the more so as S Schmidt has shown that many of the inconsistencies between the flocculation and animal

tests vanish if the mixtures are allowed to stand long enough to come to equilibrium before injection into animals

Let us pursue the analogy between the precipitin and toxin-antitoxin reactions by once more considering the Danysz phenomenon, according to which a volume of toxin, added all at once to an equivalent amount of antitoxin is just neutralized by the antitoxin, but proves excessive if added fractionally To Danysz, in 1902, this was clear evidence that toxin and antitoxin could combine in more than one proportion, just as we have found for antigen and antibody in the precipitin reaction, and this simple explanation of the effect was supported by additional tests to which he subjected it Why, then, has the Danysz effect come to be quoted either as evidence for the adsorptive nature of toxin-antitoxin union, or as so puzzling that S Schmidt, now working on the subject in Madsen's laboratory, finds himself unable to offer an explanation? The reason, I think, lies in the incorporation of Danysz's interpretation into both of the dominating but incompatible theories held at the time by Ehrlich and Bordet, and the conflict of Danysz's idea with the views of Arrhenius Ehrlich, although insisting that the combination between toxin and antitoxin was chemical, believed toxin to be a mixture of many components of different toxicities and different capacities for combination with antitoxin He therefore seized upon the Danysz effect as supporting his conception Bordet, believing that antigen and antibody reacted by adsorption in an unlimited variety of proportions, saw in the Danysz effect and in the similar effect he had observed in hemolysis only confirmation of his theory Arrhenius apparently strove to keep his idea of a reversible chemical equilibrium as simple as possible and refused to admit the complication that toxin and antitoxin could combine in more than one proportion Small wonder, then, that the interpretation that seemed so obvious to Danysz survived only precariously—adsorbed, as it were, to another theory Arrhenius, to reconcile the Danysz effect with his theory that the toxin-antitoxin reaction resembled the neutralization of a weak acid, found it necessary to invoke a new hypothesis of a slow molecular change in the antitoxin possible only in the presence of toxin or toxin-antitoxin, and involving a strengthening of the chemical union In support of this he says "the strongly toxic solutions in

which tetanolysin has been added in fractions slowly lose their abnormal toxicity, and in about six hours at 37° they are no more toxic than the corresponding mixtures which have not been fractionated" But this is exactly what would be predicted if toxin and antitoxin could combine, as Danysz maintained, in multiple proportions, and if the equilibrium at the equivalence point were reversible, as Arrhenius himself believed, and as we have shown to be the case for the analogous precipitin reaction And in much the same way many of the difficulties recently encountered by students of the toxin-antitoxin reaction might have been predicted and may be simply explained if the analogy between the precipitin and toxin-antitoxin reactions be assumed to hold True, we have pointed this out in one instance before, but having done no work ourselves on the toxin-antitoxin reaction beyond the necessary calculations, we have been very properly denounced in one quarter and ignored in another

I have tried to show how chemistry has made a beginning toward giving more definite meaning to the concepts *antigen* and *antibody* and a better understanding of the mechanism of the immune reactions in which they participate The introduction of known chemical groups into the protein molecule, with its consequent sensitive control of specificity, and the recognition of the large part played by polysaccharides in bacterial specificity have served to emphasize the essentially chemical and ultimately minutely determinable basis of biological specificity, and have simplified and clarified relationships and provided powerful aids for further progress With highly purified antibody close at hand, and with plausible theories as to its formation, the manifold problems connected with antibodies should be well on their way toward solution With these newer aids it has already been possible to obtain strong evidence of the chemical union of antigen or hapten with antibody in multiple proportions, and to express this union in terms of the laws of classical chemistry On this foundation there are now accessible new and absolute quantitative methods which should be useful tools in the acquisition of a final complete understanding of immune processes

I INTRODUCTION

Recent advances in the physiology of the autonomic nervous system have established the importance of reflexes in the control of the circulation The rather unique function of the vasomotor depressor nerves has been revealed mainly through the earlier observations of Parry (1), Waller (2), Czermak (3), de Cyon (4), and Ludwig (5), and through the more recent experimental and morphologic studies of Hering (6), Heymans (7), de Castro (8), and Koch (9) Whether an abnormal state of this reflex regulatory mechanism plays a rôle in disease has yet to be learned

The observations on patients to be described in this communication demonstrate that the abnormal state of the carotid sinus is responsible for certain symptom complexes in man

A The mechanism of the carotid sinus

Caleb Hillier Parry (1) in 1799, reporting his studies on angina pectoris, casually mentions his observations "In patients, whose hearts have been beating with undue quickness and force, I have often, in a few seconds, retarded their motions many pulsations in a minute, by strong pressure on one of the carotid arteries" " this compression of the carotid does actually accumulate blood in the aorta and heart"

Waller (2) in 1862 described more precisely the effect of pressure induced over the carotid artery behind the ramus of the lower jaw of man "The heart at first increases in number with decreased power followed by a retardation of the heart action of about 4 to 5 beats a minute " He attributed the effect of the pressure to irritation of the vagus and the sympathetic nerve As one of his conclusions he states "It is easily ascertained that the symptoms above described are not owing to compression of the carotid artery, as they may be produced without obliterating the calibre of the artery, or *vice versa* the course of the blood may be completely interrupted in the artery without producing any of the symptoms enumerated"

Czermak (3) in 1866 independently described similar observations on himself, noting that pressure on his right carotid artery at about the level of the upper margin of the sternocleidomastoid muscle produced a

temporary slowing of the heart rate He also noticed a swelling of the artery in this area, and therefore attributed the slowing of the heart to the mechanical stimulation of the vagus trunk by the adjacent bulb like dilatation of the carotid artery His interpretation was accepted for over half a century by physiologists and clinicians, and the commonly observed temporary slowing of the heart in man after pressure over the upper lateral portion of the neck was named "vagus pressure test" (*Vagus Druckversuch*) In 1923, however, Hering (6) demonstrated the same degree of slowing of the heart rate in animals when mechanical pressure was induced directly on the bifurcation of the common carotid artery, even after the vagus was separated from the artery Thus Czermak's interpretation was conclusively proved to be incorrect It was this simple observation of Hering's, followed by further studies by him, and later by his associate, Koch (9), by Heymans and his associates (7), and by de Castro (8), which demonstrated that the dilated portion of the bifurcating common carotid artery (carotid sinus) is richly supplied with sensory receptors which terminate in characteristic menisci These menisci, particularly rich in the adventitia, emerge from the adventitia as spiral fibers and leave the sinus as the sinus nerve of Hering, or the intercarotid nerve of de Castro According to the careful histologic study of Sunder-Plassmann (10), the intercarotid nerve of de Castro corresponds to the "ramus caroticus hypoglossi" of the older anatomists and to the "ramus descendens hypoglossi" of Druner This nerve joins the glossopharyngeal nerve, and in some animals, communications also exist with the vagi, the cervical gangha, and the hypoglossal nerves Thus afferent direct nerve connection is present between the carotid sinus and the medullary centers

It has been repeatedly shown that variation of localized mechanical pressure within the carotid sinus of animals produces prompt changes in the systemic arterial pressure and the heart rate If the carotid sinus is denervated, the same changes in the intrasinal pressure are ineffective Thus the afferent portion of this regulatory reflex, located in the nerve structures of the carotid sinus described above, carries impulses to the central nervous system which, in turn, through efferent channels induce peripheral vasodilatation, slowing of the heart, and fall in the arterial pressure if the pressure within the sinus

is raised, and vasoconstriction, increased heart rate, and rise in the blood pressure if the intrasinal pressure is lowered The slowing of the heart is mainly due to a reflex increase in the efferent vagus tone although, as shown recently by Regniers (11), there also occurs simultaneously an inhibitory action of the carotid sinus on the tonus of the cardiac accelerator nerves The vasodilatation, through nerve pathways and perhaps through hormonal regulation, involves large vascular areas, including the splanchnic and probably the cerebral vessels The change in the blood pressure is the combined result of the changes in the heart rate and in the vasomotor tonus That the fall in the arterial pressure may be the result of a depressor vascular reflex alone, without associated cardiac slowing, is proved by the fact that following double vagotomy or administration of atropine the fall in the blood pressure can persist in the absence of slowing of the heart

A quantitative interrelation between the pressure changes within the carotid sinus and the degree of alteration in the heart rate and arterial blood pressure in different species of mammals was demonstrated by Koch (9) and by Heymans and Bouckaert (12) Hering (6) and Koch (9) maintained that the nervous mechanism of the carotid sinus acts by exerting a tonic inhibitory influence over the bulbar vasomotor and other centers Increase in the intrasinal pressure gives rise to active tonic inhibitory impulses, while a decrease in pressure causes these afferent impulses to subside, and the medullary centers to overact

In addition to these direct regulatory effects of the carotid sinus on the circulation, there exist a number of functions of the sinus that indirectly influence the circulation Heymans (7), using Tournade's technique, demonstrated that the continuous secretion of adrenalin is reflexly controlled by the afferent aortic and sinus nerves In the carotid sinus we have, therefore, an example of a nervous mechanism which controls the circulation not only directly, but indirectly through chemical regulation An important correlation between the carotid sinus and the respiration has also been clearly demonstrated by Heymans and his coworkers (7) and by Schmidt (13)

B The function of the carotid sinus in man

References have already been made to certain observations in man, in order to understand more precisely the rôle of the carotid sinus in health and in disease, it seems desirable to consider the scattered information that is available on its function in man This is particularly important, as the function of the sinus varies in different species of animals

Since Waller's and Czermak's early observations, numerous studies on the effect of pressure over the carotid arteries have been made in man, but these investigations were performed with the intention of stimulating the vagus mechanically and therefore without a properly localized stimulation of the carotid sinus Hence the results can not be looked upon as supplying a reliable answer as to the function of the carotid sinus Following Hering's discovery of the function of the carotid sinus in animals, Koch (14) studied the effect of pressure over the carotid sinus in 50 unselected patients In 28 instances, mostly in males, the test resulted in a fall in the systolic pressure, averaging 23 per cent of the initial level In women a fall in the systolic pressure seldom occurred The fall in the arterial pressure occurred independently of the slowing of the heart, and therefore it was attributed to a depressor vasomotor reflex These observations were confirmed by Hess (15) and by Mehrmann (16), who noted a particularly marked fall in the arterial pressure in cases with arteriosclerosis or with hypertension Danielopolu (17) and Tomanek (18) observed either a rise or a fall in the arterial blood pressure following mechanical stimulation of the carotid sinus They claimed that two types of carotid sinus reflex exist in man, namely, a pressor and a depressor reflex Mandelstamm and Lifschitz (19) rightly emphasized that the results reported in the literature following stimulation of the carotid sinus in man are due in part to the faulty *technique* of this apparently simple test They pointed out that the test must always be performed under identical conditions The patient should be lying on his back, with his head elevated and slightly overhanging a support If the head is then turned somewhat to one side, the sinus is usually located just below the angle of the jaw corresponding to the upper level of the thyroid cartilage Variations in its location, however, are not uncom-

is raised, and vasoconstriction, increased heart rate, and rise in the blood pressure if the intrasinal pressure is lowered The slowing of the heart is mainly due to a reflex increase in the efferent vagus tone although, as shown recently by Regniers (11), there also occurs simultaneously an inhibitory action of the carotid sinus on the tonus of the cardiac accelerator nerves The vasodilatation, through nerve pathways and perhaps through hormonal regulation, involves large vascular areas, including the splanchnic and probably the cerebral vessels The change in the blood pressure is the combined result of the changes in the heart rate and in the vasomotor tonus That the fall in the arterial pressure may be the result of a depressor vascular reflex alone, without associated cardiac slowing, is proved by the fact that following double vagotomy or administration of atropine the fall in the blood pressure can persist in the absence of slowing of the heart

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sis, but whose arterial blood pressure was below 160 mm Hg systolic and below 90 mm diastolic

The results of these observations are essentially in agreement with those of Mandelstamm and Lifschitz (19) The most significant findings were that in persons with normal cardiovascular system the response was absent in 30 per cent of the cases, in the rest there was a fall in the systolic and diastolic arterial blood pressure of less than 10 mm Hg and very little slowing of the heart (fig 1) In 55 per cent of the cases the slowing of the heart either was absent or was less than 6 beats per minute In the group of patients with hypertension, 78 per cent showed a drop in the systolic blood pressure of from 10 to 105

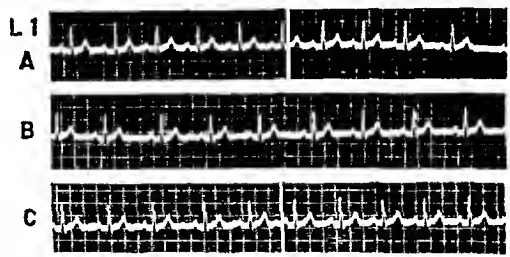

FIG 1 A case with normal cardiovascular system, and with normal response to carotid sinus pressure Electrocardiogram Lead I *A*, *B* and *C* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of pressure on the right carotid sinus Note the very slight slowing

mm Hg, with an average of 40 mm The fall in the diastolic pressure varied up to 40 mm Hg, with an average of 18 mm Hg The slowing of the heart in 70 per cent of the cases varied from 4 to 20 beats per minute, with an average of 8 In the arteriosclerotic group without hypertension 80 per cent showed a drop in systolic blood pressure of from 10 to 65 mm Hg, with an average of 30 mm The fall in the diastolic pressure varied from 5 to 35 mm Hg, with an average of 25 mm The slowing of the heart varied from 6 to 28 beats per minute, with an average of 16 beats No correlation existed between the cardiac slowing and the fall in blood pressure in a given case

In the groups with hypertension and arteriosclerosis, dizziness followed at times firm and prolonged pressure In no instance, however,

mon We have observed 2 cases in which the dilated sinus was located at the level of the larynx on one side and higher on the other side If over the sinus area pressure is induced toward the spinal column, a characteristic depressor response of 10 to 20 seconds' duration can often be elicited

Mandelstamm and Lifschitz demonstrated that such a stimulation of the sinus nerve in man results in a true depressor nerve reflex They succeeded in inducing a fall in systolic pressure of at least 10 mm Hg in 60 per cent of 335 cases The degree of fall was particularly marked in patients with arteriosclerosis and with hypertension Thus in 103 aged and retired Russian workers the average fall in systolic blood pressure was 37 mm Hg, while in 106 healthy soldiers it was only 5 mm Hg They found that a parallelism between the degree of slowing of the heart and the fall in blood pressure did not necessarily exist, frequently fall in the blood pressure occurred without slowing of the heart rate The fall in the blood pressure lasted but a few minutes in the majority of instances, but it was usually of longer duration than the slowing of the heart Repeated tests always resulted in similar responses under identical experimental conditions These investigators failed to find a difference between the effect of the stimulation of the right and of the left sinus They noted that the intensity of the responses was the same in both sexes

II OBSERVATIONS

A In normal subjects and in patients with primary arterial hypertension, with arteriosclerosis, and with abnormality of the heart

During the past 4 years one of us has tested routinely the effect of mechanical stimulation of the carotid sinus in several hundred ward and ambulatory patients by means of a technique similar to that used by Koch (9) and by Mandelstamm and Lifschitz (19) As control, pressure below the sinus was applied Record of the changes in blood pressure and heart rate was kept in 128 cases (*a*) 50 patients with normal cardiovascular systems, (*b*) 42 patients with arterial hypertension, having a systolic pressure of from 180 to 260 mm Hg and a diastolic pressure of from 90 to 170 mm Hg, in whom arteriosclerosis was either absent or present in varying degree, and (*c*) 36 patients over 50 years of age in whom the primary diagnosis was arteriosclero-

B The syndrome dizziness, fainting and convulsions due to hyperactive carotid sinus reflex

We have studied 15 patients, who, with two exceptions, complained of spontaneous attacks of dizziness and fainting and in whom pressure of graded severity on one or on each carotid sinus produced dizziness, fainting and convulsive seizures These cases were found among a large group of patients suffering from various diseases associated with fainting or convulsions The observations to be presented not only throw light on the mechanism underlying the clinical manifestations of dizziness, fainting and convulsions, but they also reveal the nature of the mechanism of the carotid sinus reflex in man

We have observed certain definite pathologic changes in the carotid sinus and changes in the circulatory and nervous systems resulting from stimulation of the carotid sinus by pressure These abnormalities will be taken up in the following order (1) subjective symptoms such as dizziness, blurring of vision, ringing in the ears, and objective signs such as pallor, fainting and convulsions, (2) gross changes in the structure of the sinus, (3) effect of bodily posture on the symptoms, (4) slowing of the heart rate, (5) fall in arterial blood pressure, (6) electrocardiographic changes, (7) diminution in cardiac output and increase in circulation time, (8) changes in the gaseous content of the blood obtained from the internal jugular vein In addition, we have studied the effect on the reflex of certain pharmacologic agents, and in two instances the effect of therapeutic section of the intercarotid nerve These changes occurred in various combinations in different patients A summarized report of the cases is appended to this communication

1 Symptoms and signs These depended in the majority of cases upon a marked slowing of the heart, or a fall in blood pressure or both Where the blood pressure fell but little, fainting and convulsions occurred after asystole lasting for from 7 to 10 seconds Cases showing marked hyperactivity of the sinus exhibited contralateral convulsions on mild stimulation and generalized convulsions following stronger stimulation In all cases convulsive movements were preceded by a state of unconsciousness, which came on suddenly or slowly, depending on the degree of pressure, and was often preceded by

TABLE 1

Symptoms and signs resulting from pressure on the carotid sinus

PATIENT	SINUS STIMULATED	SYMPTOMS	SIGNS
1	Right	Dizziness, blurring of vision, faintness	Slowing of pulse, fall in blood pressure (marked), pallor, hyperpnea, unconsciousness, convulsions (chiefly unilateral)
	Left	Slight dizziness	Slowing of pulse, fall in blood pressure, no convulsions or fainting
2	Right	Dizziness, blurring of vision, faintness	Asystole, marked slowing of pulse, fall in blood pressure (moderate), pallor, hyperpnea, unconsciousness, convulsions (bilateral)
	Left	Same	Same
3	Right	Dizziness, "music in ears," blurring of vision	Slowing of pulse, fall in blood pressure (marked), pallor, hyperpnea, unconsciousness, convulsions (bilateral)
	Left	Same, but less marked	Same, but less marked
4	Right	None	Moderate slowing of pulse, no fall in blood pressure
	Left	None	Slight slowing of pulse
5	Left	Dizziness, blurring of vision, faintness	Asystole, slowing of pulse, fall in blood pressure (moderate), pallor, unconsciousness, convulsions (bilateral)
	Right	None	Slowing of pulse, fall in blood pressure (moderate), no fainting or convulsions
6	Left	Dizziness, blurring of vision, faintness	Asystole, slowing of pulse, hyperpnea, convulsions (unilateral), no fall in blood pressure
	Right	Same, but much less marked	Same, but much less marked
7*	Right	None	A-V block, regular ventricular rhythm, no fall in blood pressure
	Left	None	Same
8	Right	Dizziness, blurring of vision, "dead feeling" in left arm	Listless expression, pallor, perspiration, fainting, no slowing of pulse or fall in blood pressure
	Left	None	None
9	Right	Dizziness, blurring of vision	Slight slowing of pulse, pallor, no fall in blood pressure
	Left	None	None

* Fibrillating

TABLE 1—*Concluded*

PATIENT	SINUS STIMULATED	SYMPTOMS	SIGNS
10	Right	Dizziness, blurring of vision, faintness	Asystole slowing of pulse fall in blood pressure (moderate), aphasia, unconsciousness, convulsions (bilateral)
	Left	Same	Same
11	Right	Dizziness, sees "black spots in front of eyes"	Slight fall in blood pressure, pallor, unconsciousness, twitching of the left hand, no slowing of pulse
	Left	Same	Same, but not so marked
12	Right	Dizziness, blurring of vision	Marked slowing of pulse, fall in blood pressure, pallor, hyperpnea, unconsciousness convulsions (unilateral)
	Left	Same	Same but not so marked
13	Right	Dizziness blurring of vision	Marked slowing of pulse and fall in blood pressure, fainting
	Left	Same	Same
14	Right	Dizziness blurring of vision, headache	Slight slowing of pulse fainting and convulsions (unilateral), no fall in blood pressure
	Left	None	None
15	Right	Dizziness darkening of vision	Slowing of pulse, fall in blood pressure pallor, hyperpnea, unconsciousness convulsions (unilateral)
	Left	Same	Same

characteristic aurae such as epigastric discomfort, ringing in the ears or visual hallucinations In order to induce minimal discomfort, the pressure over the sinus was usually released at the onset of the first clonic movements Three of the cases (Nos 8, 9 and 14) showed the usual striking clinical symptoms and signs from stimulation of the sinus, although they had little or no slowing of the heart or fall in blood pressure In these cases fainting and convulsions were associated with marked pallor of the face followed by an intense cyanotic flush Control observations with the same degree of pressure over the carotid artery below the sinus were performed frequently and failed to induce symptoms and signs Table 1 summarizes the symptoms and signs resulting from pressure on the carotid sinus in the cases studied

2 Pathology Hyperactivity of any reflex may be caused by in

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3	Right	Dizziness, "music in ears," blurring of vision	Slowing of pulse, fall in blood pressure (marked), pallor, hyperpnea, unconsciousness, convulsions (bilateral)
	Left	Same, but less marked	Same, but less marked
4	Right	None	Moderate slowing of pulse, no fall in blood pressure
	Left	None	Slight slowing of pulse
5	Left	Dizziness, blurring of vision, faintness	Asystole, slowing of pulse, fall in blood pressure (moderate), pallor, unconsciousness, convulsions (bilateral)
	Right	None	Slowing of pulse, fall in blood pressure (moderate), no fainting or convulsions
6	Left	Dizziness, blurring of vision, faintness	Asystole, slowing of pulse, hyperpnea, convulsions (unilateral), no fall in blood pressure
	Right	Same, but much less marked	Same, but much less marked
7*	Right	None	A-V block, regular ventricular rhythm, no fall in blood pressure
	Left	None	Same
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	Left	Same	Same, but not so marked
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	Left	Same	Same
14	Right	Dizziness blurring of vision, headache	Slight slowing of pulse, fainting and convulsions (unilateral), no fall in blood pressure
	Left	None	None
15	Right	Dizziness, darkening of vision	Slowing of pulse fall in blood pressure pallor hyperpnea unconsciousness convulsions (unilateral)
	Left	Same	Same

characteristic aurae such as epigastric discomfort, ringing in the ears or visual hallucinations In order to induce minimal discomfort, the pressure over the sinus was usually released at the onset of the first clonic movements Three of the cases (Nos 8, 9 and 14) showed the usual striking clinical symptoms and signs from stimulation of the sinus, although they had little or no slowing of the heart or fall in blood pressure In these cases fainting and convulsions were associated with marked pallor of the face followed by an intense cyanotic flush Control observations with the same degree of pressure over the carotid artery below the sinus were performed frequently and failed to induce symptoms and signs Table 1 summarizes the symptoms and signs resulting from pressure on the carotid sinus in the cases studied

2 Pathology Hyperactivity of any reflex may be caused by in-

ceased irritability of the afferent or efferent nerve endings, or of the central synapses, either alone or combined. In 6 cases a definite aneurysmal dilatation of one or both carotid sinuses was noted; in 3 cases a small tumor pressing on the sinus was found; and in the remaining 6 cases no gross pathology was detected. The appearance

Fig. 4. Specimen from case 6, who died from lobar pneumonia. (Note the group of lymph nodes surrounding the bifurcation of the carotid artery (left).) The carotid sheath has been dissected to show the vagus.

of one of the sinuses surrounded by lymph nodes in a patient who died from lobar pneumonia is shown in figures 4 and 5.

3. Effect of bodily posture. Pressure on the carotid sinus brought on fainting more quickly when the patient was sl

when he was lying down In case 2 we measured repeatedly the time interval between stimulation of the sinus and the onset of fainting in various positions of the body With the head down and the body and feet elevated at an angle of 30° the attack was brought on in 30 seconds, with the patient horizontal, in 10 seconds, with the patient standing, in 8 5 seconds

FIG 5 Same specimen as figure 4 The group of lymph nodes has been removed to show the bulbous dilatation of the internal carotid artery—the carotid sinus

4 *Slowing of the heart rate* This was present, in some degree, in all except 3 of the cases In several of the patients studied there was cardiac standstill lasting 2 to 12 seconds, followed by a slow rate as long as the pressure was applied The onset and disappearance of the slowing immediately followed the application and relief of pressure (chart 1) The greatest slowing always occurred directly after pressure was applied, thereafter the rate became more nearly normal, even though pressure was continued Table 2 presents the effect of

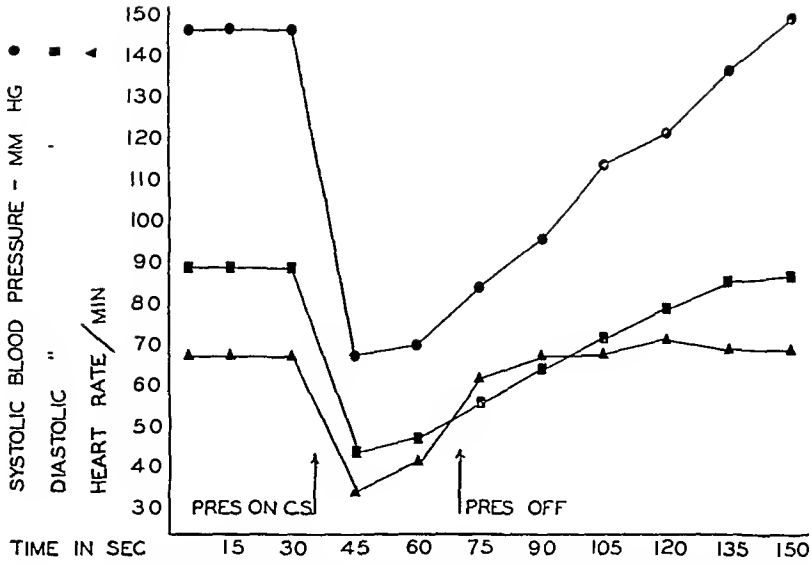


CHART 1 The effect on heart rate and blood pressure of pressure on the carotid sinus (case 1) Note that both heart rate and blood pressure show a marked fall immediately after stimulation of the sinus When pressure is released, the heart rate returns to normal very quickly, the blood pressure more slowly

TABLE 2

Effect on heart rate of pressure on the carotid sinus

PATIENT	NORMAL HEART RATE PER MINUTE	PRESSURE RIGHT CAROTID SINUS		PRESSURE LEFT CAROTID SINUS	
		Maximal asystole duration	Heart rate per minute after asystole	Maximal asystole duration	Heart rate per minute after asystole
		seconds		*seconds*	
1	64–72	3†	36–42	None	36–42
2	90–110	10	5–15	12	10–30
3	56–60	3†	38–50	None	38–50
4	80–84	None	40–45	None	70–75
5	90–96	2	80–90	5	50–60
6	75–80	None	65–70	4	30–50
7	75–80*	None	60	None	60
8	100–108	None	100–108	None	100–108
9	90–96	None	75–80	None	90–96
10	72–80	8	40–50	5	40–50
11	68–72	None	68–72	None	68–72
12	100	None	60	None	64
13	72	None	Slowed markedly	None	Slowed markedly

* Fibrillating

† Not always present

ırotid sinus pressure on the heart rate in this group of cases The ıtensity of pressure often had a direct bearing on the degree of slow- ıg In the most sensitive cases even the slightest manipulation of

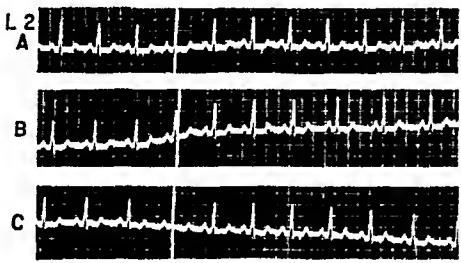


Fig 6 Case 2 Electrocardiogram Lead II The vertical white line in *A* represents ressure on both supraorbital nerves, in *B*, pressure on the abdominal aorta, and in *C*, ressure on the right femoral artery There was no appreciable slowing in any case

TABLE 3

Blood pressure changes due to stimulation of the carotid sinus

PATIENT	NORMAL		PRESSURE RIGHT CAROTID SINUS		PRESSURE LEFT CAROTID SINUS	
	Arterial blood pressure					
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
	mm Hg	*mm* Hg	*mm* Hg	*mm* Hg	*mm* Hg	*mm* Hg
1	140	72	98	?	72	60
2	160	80	115	75	115	75
3	128	68	70	?	85	50
4	176	90				
5	134	72	90	?	90	?
6	145	30	140	30	140	30
7	175	100	150	90	150	90
8	106	54	106	54	106	54
9	114	72	114	72	114	72
10	125	75	98	64	96	64
11	108	78	78	50	84	60
12	148	90	70	55	42	?
13	110	70	50	30	50	30

the skin over and around the sinus induced cardiac slowing Pressure over the eyeballs, abdominal aorta, and femoral arteries induced almost no slowing in cases where this was tried (fig 6)

5 Fall in arterial blood pressure The fall in arterial blood pressure was not always related to cardiac slowing The degree of fall showed wide variations Like the heart rate, the greatest fall in the blood

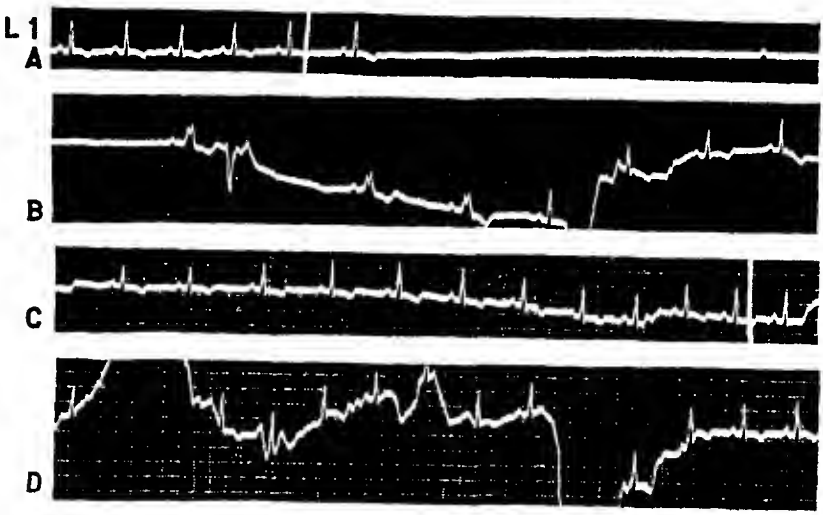


FIG 7 Case 2 Electrocardiogram Lead I *A*, *B*, *C* and *D* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of pressure on the carotid sinus Note the long period of cardiac standstill followed by a slower rate and wide ventricular complexes The wavy tracing in *D* indicates a mild convulsion, with recovery at the end of the tracing

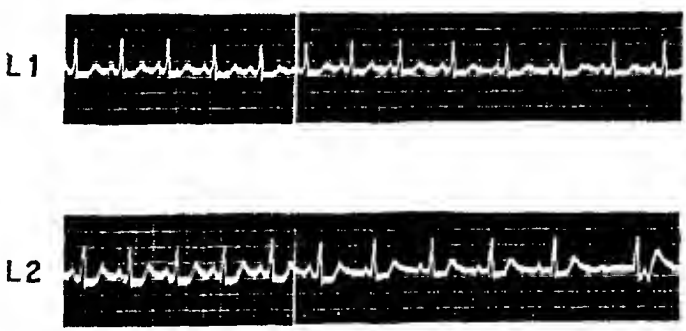


FIG 8 Case 2 Electrocardiograms Leads I and II Vertical white lines indicate beginning of slight pressure on the carotid sinus Note in Lead II the prolongation of the P-R interval

pressure came immediately after the pressure was applied The return to normal, on the other hand, occurred relatively slowly (chart 1) Often not only the degree but the suddenness of the application

of pressure had a direct relation to the degree of fall Table 3 summarizes the blood pressure changes in this group of cases

6 Electrocardiographic changes The stimulation of the carotid sinus induced striking changes in the intracardiac conductive system

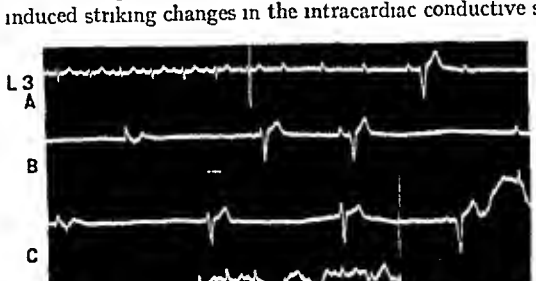


FIG 9 Case 2 Electrocardiogram Lead III *A*, *B*, *C* and *D* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of firm pressure on the carotid sinus Note complete A V block, ventricular escape and bizarre QRST complexes The wavy tracing in *C* and *D* indicates a convulsion, with recovery at the end of *D*

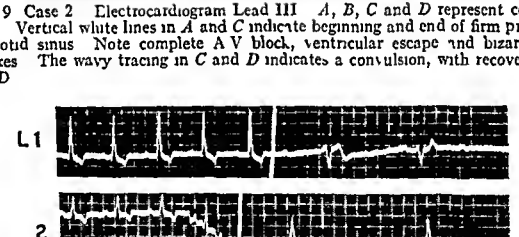


FIG 10 Case 6 Electrocardiograms Leads I, II and III Vertical white lines in each lead show beginning of carotid sinus pressure Note complete A V block and ventricular extrasystoles

These varied greatly in different patients, and even in the same patient The most profound changes observed were the long periods of cardiac standstill, during which no activity of any of the chambers

of the heart was registered (fig 7) A frequent feature of many of the electrocardiograms was evidence of block between the auricles and the ventricles, varying in degree from a prolonged P-R interval (fig 8) to complete A-V block (figs 9 and 10) In some cases, the auricles con-

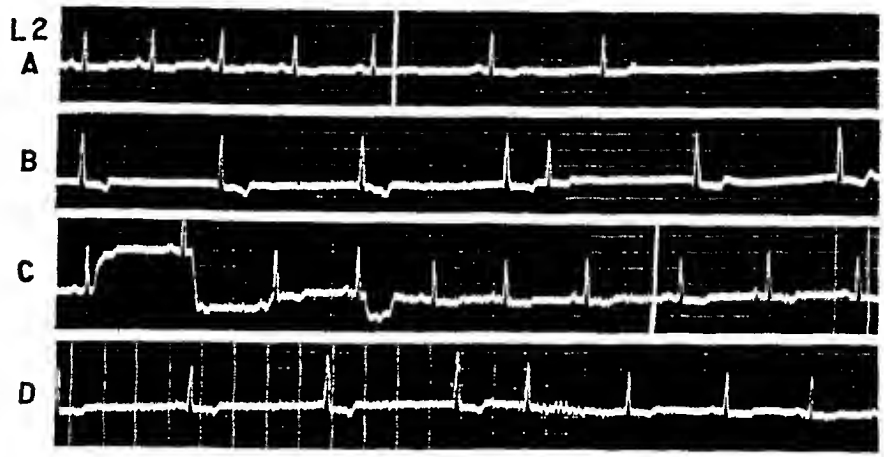


FIG 11 Case 1 Electrocardiogram Lead II *A*, *B*, *C* and *D* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of carotid sinus pressure Note the marked slowing, A-V block, and nodal rhythm The wavy tracing in *C* and *D* represents a mild convulsion, with recovery at the end of *D*

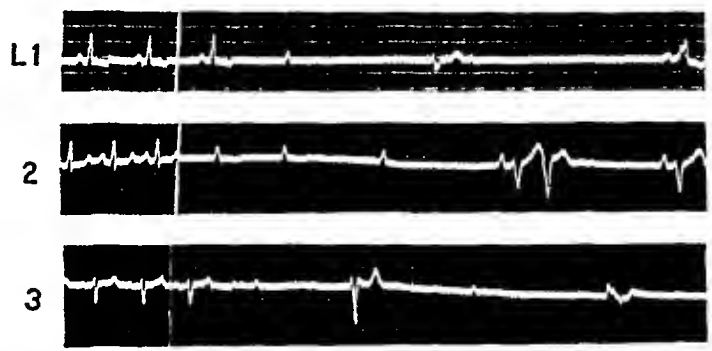


FIG 12 Case 2 Electrocardiograms Leads I, II and III Vertical white lines in each lead indicate beginning of carotid sinus pressure Note A-V block, ventricular extrasystoles, and bizarre ventricular complexes

tinued to beat for several seconds after the sinus was stimulated, none of the P waves being followed by QRST complexes, following this, there was evidence of ventricular activity, either as nodal rhythm, ventricular extrasystoles or bizarre complexes such as occur in ven-

tricular fibrillation (figs 11 and 12) We can not explain some of the complexes such as those shown in figures 9 and 11 In case 4 with a normal electrocardiogram, pressure on the sinus caused the ST waves

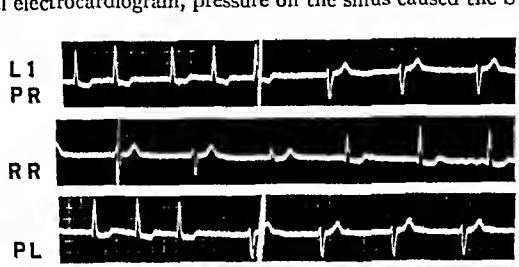


FIG 13 Case 7 Electrocardiogram Lead I Vertical white lines in *PR* and *RR* indicate beginning and end of pressure on the right carotid sinus, in *PL* and *RL* beginning and end of pressure on the left carotid sinus (the marker in *PL* was made a little late) In the control tracing, note the rhythm of auricular fibrillation, this gives way to a slow, regular, ventricular rhythm when pressure is made on the carotid sinus, but returns when pressure is released

TABLE 4

Cardiac output and dye circulation time

PATIENT		DYE CIRCULATION TIME	CARDIAC OUTPUT
		seconds	*Litres per minute*
1	Normal resting state	16	7 0
	Pressure carotid sinus	32	4 4
2	Normal resting state	18	7 5
	Pressure carotid sinus	26	6 2
3	Normal resting state	18	5 2
	Pressure carotid sinus	1[illegible]	3 6
6	Normal resting state	[illegible]	5 [illegible]
	Pressure carotid sinus	[illegible]	3 7

to become convex upward with an inverse T wave. Changes in the electrical axis also occurred (fig 13' [illegible] were associated with precordial pain [illegible]

7 Volume and velocity of blood flow These were estimated by the dye injection method described by Hamilton, Moore, Kinsman and Spurling (20) The circulation time is considered to be the time elapsing between the injection of the dye into the antecubital vein and its appearance in the femoral artery Determinations were made first while the patient was at rest and then were repeated while pressure was applied over the carotid sinus, and while there was slowing of the heart, fall in arterial blood pressure, fainting and mild convulsions The results of these determinations, which are shown in table 4, indicate that

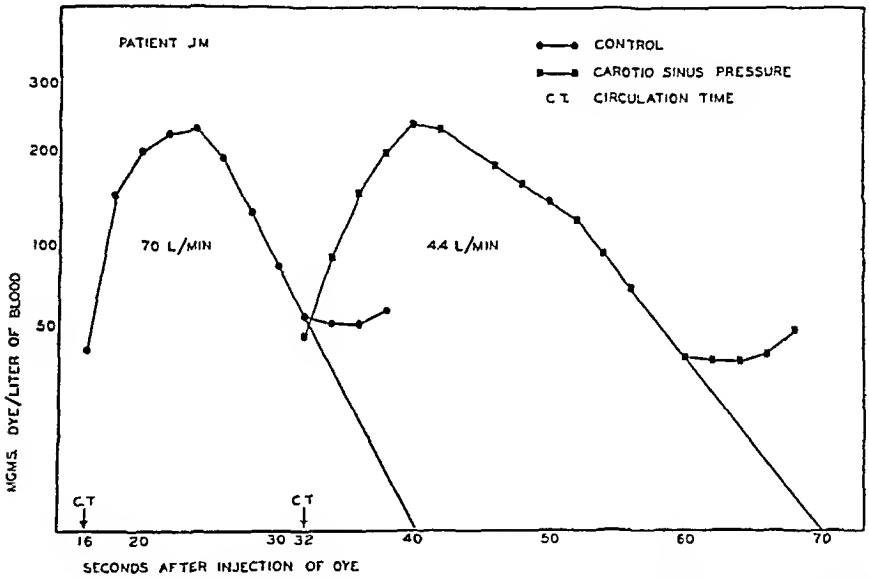


CHART 2 Case 1 Dye distribution curves in cardiac output determinations before and during carotid sinus pressure

during stimulation of the sinus there is a decrease in the cardiac output and slowing of the velocity of blood flow, but the degree of the changes varies Chart 2 shows the dye distribution curves in two cardiac output determinations in case 1

8 Cerebral circulation (*a*) *Oxygen and carbon dioxide content of blood from the internal jugular vein* According to a technique previously described (21) blood was taken, under local anesthesia, from the femoral artery and the internal jugular vein while the patient was lying quietly in bed Then, with needle in place in the internal jugular vein, pressure was applied on the opposite carotid sinus until the heart

slowed, blood pressure fell, and fainting and mild convulsions developed At the beginning of and during these symptoms a continuous sample of blood was withdrawn All samples were collected under oil The analyses were made by the method of Van Slyke These results are shown in table 5

(*b*) *Vessels of the eyegrounds* Repeated attempts have been made to compare the vessels of the eyeground before, during and after release of pressure over the sinus In some instances paling of the eyegrounds, with narrowing of the smaller vessels, followed by an increase in color and dilatation of the vessels, was thought to occur, but the changes were not striking enough to trust the observations [2]

TABLE 5

Blood gases

PATIENT		ARTERIAL BLOOD			INTERNAL JUGULAR BLOOD		
		Content		O_2 saturation	Content		A V O_2 difference
		O_2	CO_2		O_2	CO_2	
		vols per cent	*vols per cent*	*per cent*	*vols per cent*	*vols per cent*	*vols per cent*
1	Normal resting state	17 25	46 45	97	14 95	44 95	2 30
	Pressure carotid sinus				11 75	48 60	5 50
3	Normal resting state	17 11	46 30	89			
	Pressure carotid sinus				10 73	49 85	6 38
5	Normal resting state	13 16	43 30	96	8 63	47 25	4 53
	Pressure carotid sinus				7 19	48 24	5 97

9 Effect on the reflex of certain pharmacologic agents In order to ascertain the nature of the reflex, we administered drugs known to act rather specifically on the sympathetic or the parasympathetic components of the autonomic nervous system Other chemical substances were used to ascertain the relation of the reflex to the state of the minute blood vessels of the brain The nerves from the sinus were

[2] In 3 cases with normal response of the carotid sinus, in which for surgical reasons the brain surface was exposed, we observed no changes in the diameter of the blood vessels or in the color of the brain surface while pressure was applied over each of the carotid sinuses Avertin anesthesia was used in these patients So far we have had no opportunity to observe the vessels of the surface of the brain in patients with hyperactive carotid sinus reflex

TABLE 7

Effect of atropine intramuscularly

PATIENT	BEFORE ATROPINE				
	Resting		Pressure on carotid sinus		
	Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
		mm Hg		*mm* Hg	
1	64	114/82	36–48	90/72	Dizziness, fainting, pallor, convulsions
2	86	158/68	5–15	100/52	Dizziness, fainting, pallor, convulsions
3	52	128/66	38–50	70/?	"Music in ears," pallor, fainting, convulsions
6	84	142/42	30–50	132/30	Faintness, blurring of vision, convulsions
11	68	108/78	68	84/60	Dizziness, fainting, pallor

PATIENT	DOSE OF ATROPINE SULPHATE	AFTER ATROPINE				
		Resting		Pressure on carotid sinus		
		Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
	mgm		*mm* Hg		*mm* Hg	
1	5 75 (2 doses)	108	112/?	104		Blurring of vision, mild convulsion, no fainting
2	5 10 (2 doses)	100	140/70	100	125/62	Hyperpnea, no fainting or convulsions
3	5 10 (3 doses)	72	140/70	68	94/?	"Music in ears," pallor, fainting, convulsions
6	2 55 (1 dose)	84	142/40	84	140/40	No fainting, blurring of vision or convulsions
11	2 55 (1 dose)	120	116/80	120		Dizziness, fainting, pallor

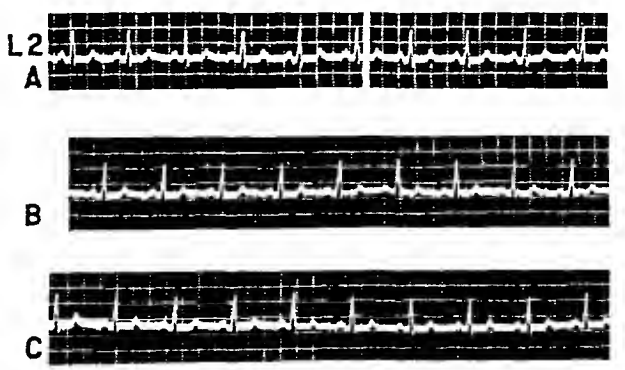


FIG 15 Case 2 Electrocardiogram Lead II *A*, *B* and *C* represent continuous tracing Vertical white line in *A* indicates beginning of pressure on the right carotid sinus after atropine Figure 7 shows the effect of right carotid sinus pressure in this same case before atropine

sympathetic endings in the wall of the sinus or on the vagus center, we compared the effect of injecting atropine into the internal carotid artery above the sinus with that produced when atropine was injected into the common carotid artery below the sinus As the results were

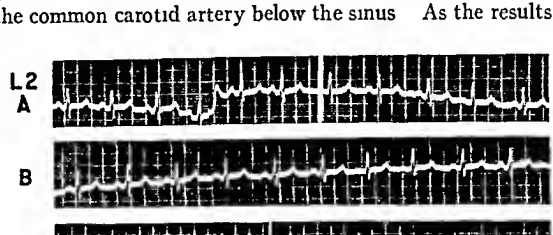


FIG 16 Case 2 Electrocardiogram Lead II *A*, *B* and *C* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of right carotid sinus pressure after the injection of 0 32 mgm atropine sulphate into the right carotid artery Figure 7 shows the effect of right carotid sinus pressure in this same case before atropine

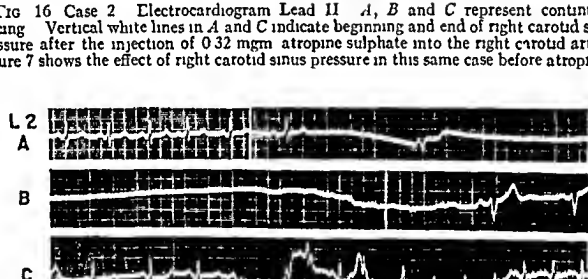


FIG 17 Case 2 Electrocardiogram Lead II *A*, *B*, *C* and *D* represent continuous tracing Vertical white lines in *A* and *B* indicate beginning and end of pressure on the left carotid sinus after the injection of 0 32 mgm atropine sulphate into the right carotid artery

the same, regardless of whether atropine was administered below or above the sinus, it is concluded that atropine exerts no local effect on the sinus, but rather acts on the ipsolateral centers of the midbrain Table 8 shows the results in 4 patients

TABLE 8

Effect of atropine in carotid artery

PATIENT	BEFORE ATROPINE					DOSE OF ATROPINE SULPHATE	AFTER ATROPINE					
	Resting		Pressure on carotid sinus				Resting			Pressure on carotid sinus		
	Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs		Heart rate per minute	Arterial blood pressure	Signs	Heart rate per minute	Arterial blood pressure	Symptoms and signs
		mm Hg		*mm* Hg				*mm* Hg			*mm* Hg	
2*	92	158/68	Right 5–15	Right 100/52	Right dizziness, pallor, fainting, convulsions	0 32 mgm in right internal carotid artery above sinus	96	146/62	Right pupil dilated	Right 92	Right—	Right none
			Left 20–30	Left 112/56	Left same but milder					Left 5–10	Left—	Left dizziness, pallor, severe convulsion, unconsciousness
3*	52	120/62	Right 38–50	Right 80/42	Right "music in ears," pallor, fainting, convulsions	0 43 mgm in right internal carotid artery above sinus	68	124/68	Right pupil dilated	Right 50	Right 70/?	Right "music in ears," pallor, fainting, convulsions
			Left 38–50	Left 90/48	Left Same					Left 30	Left 70/42	Left same
4†	84	166/90	Right 40–45	Right —	Right none	0 32 mgm in right common carotid artery below sinus	84	164/90	Right pupil dilated	Right 84	Right—	Right none
			Left 70–75	Left—	Left none					Left 70–75	Left—	Left none
6	80	144/38	Left 30–50	Left 130/32	Left dizziness, blurring of vision, convulsions	0 20 mgm in left common carotid artery below sinus	84	155/40	Left pupil dilated	Left 80	Left 150/35	Left none
			Right 65–70	Right 134/38	Right none					Right 65–70	Right 150/35	Right none

* Repeated another day with same amount of atropine in the common carotid artery below the sinus Same results

† Repeated another day with double this amount of atropine intravenously Slowing was not abolished

(*d*) *Sodium luminal* In order to determine whether the reflex could be abolished by central depression, a sufficient amount of sodium luminal was given intravenously to cause extreme somnolence The sensitivity of the reflex was not affected (table 9)

(*e*) *Novocaine block of the sinus* This was accomplished by introducing a hypodermic needle into the tissue over the sinus until the wall of the artery could be felt to pulsate against the needle Novocaine was then injected into the wall of the artery This procedure regularly blocked the reflex, as is shown by the data given in table 10 The abolition of the reflex slowing of the heart is shown in figure 18 Two objections arose as to the interpretation of these results, namely (*a*) that they were due to a systemic action of the novocaine, and (*b*) that the efferent impulses through the vagus had been blocked To test the validity of these objections we (*a*) injected the same amount of novocaine in an indifferent area of the neck, and (*b*) infiltrated with

TABLE 9

Effect of sodium luminal intravenously

PATIENT	BEFORE LUMINAL				
	Resting		Pressure on carotid sinus		
	Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
		mm Hg		*mm* Hg	
1	76	128/92	36–42	90/72	Dizziness, fainting, pallor, convulsions
2	100	180/94	5–15	142/60	Dizziness, fainting, pallor, convulsions

PATIENT	DOSE OF SODIUM LUMINAL	AFTER LUMINAL				
		Resting		Pressure on carotid sinus		
		Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
	mgm		*mm* Hg		*mm* Hg	
1	455 (2 doses)	76	124/94	36–42	76/65	Dizziness, fainting, pallor, convulsions (slept soundly for 4 hours)
2	455 (1 dose)	104	176/92	5–15	130/?	Dizziness, fainting, pallor, convulsions (slept soundly for 3 hours)

TABLE 10

Novocainization of carotid sinus

PATIENT	BEFORE NOVOCAINIZATION				
	Resting		Pressure on carotid sinus		
	Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
		mm Hg		*mm* Hg	
1	72	120/72	36–40	58/?	Dizziness, fainting, pallor, convulsions
2	100	150/70	5–15	100/46	Dizziness, fainting, pallor, convulsions
6	76	145/30	30–50	140/30	Faintness, blurring of vision, convulsions

PATIENT	AFTER NOVOCAINIZATION				
	Resting		Pressure on carotid sinus		
	Heart rate per minute	Arterial blood pressure	Heart rate per minute	Arterial blood pressure	Symptoms and signs
		mm Hg		*mm* Hg	
1	80		76	116/?	No dizziness, fainting, pallor or convulsions
2	100	156/70	100	160/68	No dizziness, fainting, pallor or convulsions
6	80	150/42	80	144/42	No faintness, blurring of vision or convulsions

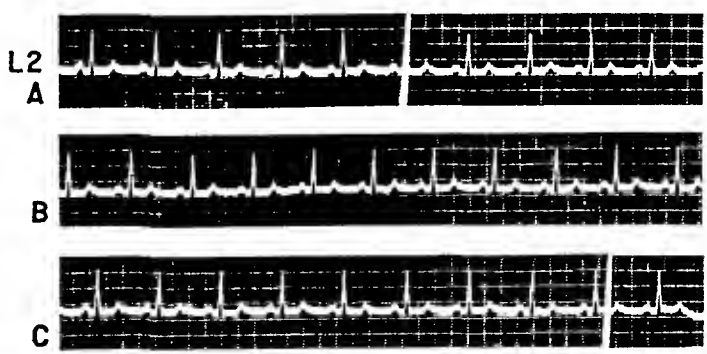


FIG 18 Case 2 Electrocardiogram Lead II *A*, *B* and *C* represent continuous tracing Vertical white lines in *A* and *C* indicate beginning and end of pressure on the right carotid sinus after novocaine block Figure 7 shows the effect of right carotid sinus pressure in this same case before novocaine block

novocaine around the carotid artery low in the neck Both these procedures had no effect on the reflex

(*f*) *The effect of unilateral section of the intercarotid nerve* In case 1 suffering from fainting attacks, in whom a small localized, sharply circumscribed tumor pressed on the right sinus, surgical removal of the tumor and section of the intercarotid nerve was performed Before operation, pressure on the right sinus caused fainting and convulsive seizures, associated with marked slowing of the heart rate and fall in blood pressure (fig 11 and chart 1), stimulation of the left sinus was ineffective The observations during and after operation afforded an opportunity to study the effect of section of the nerves of a hypersensitive sinus The operation, performed by Dr Tracy J Putnam, was done under novocaine anesthesia, preceded by morphine and hyoscine The sinus was exposed and a small soft mass removed The sinus and the artery above and below were then stripped, thus assuring severance of the carotid nerve Following denervation of the sinus, there was an immediate sharp rise in the blood pressure which persisted for about 36 hours After the carotid sinus was stripped, pressure on it did not elicit the usual reflex The right vagus was identified at operation and stimulated repeatedly by pinching, there was no slowing of the heart or fall in blood pressure or any of the symptoms which had previously been observed from pressure on the carotid sinus Immediately after the operation, numerous extrasystoles were noticed These persisted for a day, after which the pulse became totally irregular An electrocardiogram at this time showed auricular fibrillation (fig 19), which persisted for 7 days The heart rhythm then returned spontaneously to normal (fig 20) The outstanding changes during and following the operation are shown in chart 3

In addition to the direct section of the intercarotid nerve, we have had opportunity to observe the effect of the unilateral *section of the glossopharyngeal nerve* close to its entrance into the medulla In a patient aged 61, who suffered from carcinoma of the tonsil, in order to relieve the pain the right glossopharyngeal nerve close to the foramen of exit inside the dura was cut by Dr Donald Munro Avertin and local novocaine anesthesia was used The average blood pressure before the section was 95 mm systolic and 65 mm diastolic Within 5 minutes after the section the blood pressure rose to 175 systolic and

100 diastolic In the course of about 40 minutes this pressure gradually returned to a level of 115 systolic and 75 diastolic The pain was completely relieved and examination following operation revealed complete ninth nerve anesthesia As the intercarotid nerve usually enters the brain stem mainly through the glossopharyngeal nerve, this observation indicates that sectioning of the ninth nerve close to the brain stem may result in vasomotor reaction In another case

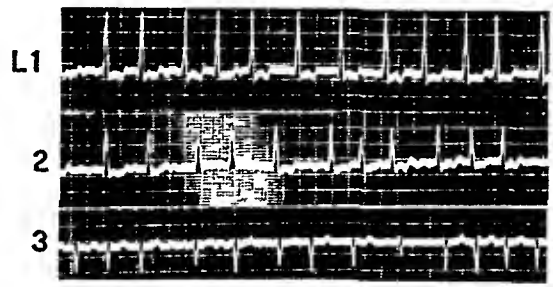


FIG. 19 Case 1 Electrocardiograms Leads I, II and III Auricular fibrillation developing 2 days after section of the right intercarotid nerve Electrocardiogram in this case before operation shown in figure 11

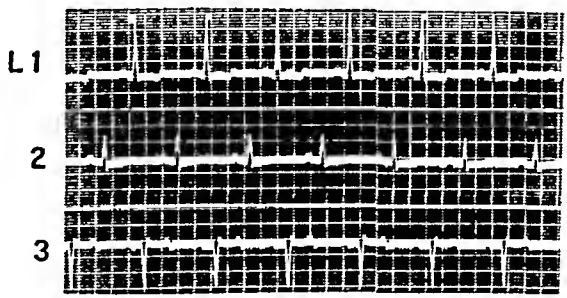


FIG 20 Case 1 Electrocardiograms Leads I, II and III Spontaneous return to normal rhythm 7 days after the onset of auricular fibrillation

in which carcinoma of the tongue existed, section of the glossopharyngeal nerve for relief of pain resulted also in a vasomotor response, but other complicating factors make the evaluation of this section uncertain

(g) *Dilatation of the cerebral vessels with histamine, acetylcholine and carbon dioxide* These substances are dilators of the cerebral vessels (22) (23) (24) In 3 of the patients (cases 2, 3 and 11) who showed

the sinus reflex markedly, we gave inhalations of 10 per cent carbon dioxide and 90 per cent oxygen until a marked degree of hyperpnea with flushing of the face was attained At this time, pressure on the carotid sinus brought on the reflex changes as pronouncedly as before In 2 of these patients (cases 2 and 3) infusions of histamine and acetylcholine intravenously did not abolish the reflex Finally, minute amounts of these drugs, greatly diluted with saline, were

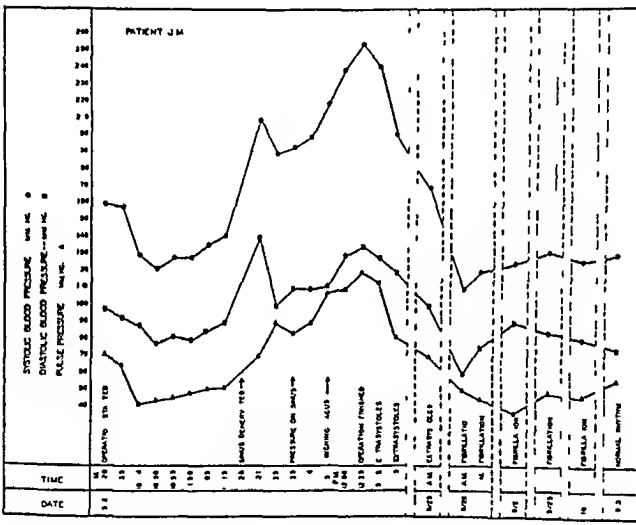


CHART 3 Case 1 The effect on blood pressure and cardiac rhythm of section of the right intercarotid nerve

injected into the carotid artery on the side which showed the more sensitive reflex There resulted regularly a unilateral flushing of the face and sensation of smarting in the head At the height of this effect, the needle was withdrawn and pressure was immediately applied on the carotid sinus The reflex changes followed as before Thus the reflex was uninfluenced even under ideally arranged cerebral arterial vasodilatation

III DISCUSSION

A The evidence that the clinical manifestations are due to a hypersensitive carotid sinus reflex and not to direct vagal stimulation

The following evidence supports definitely the belief that the clinical manifestations presented are due to overactive carotid sinus reflex and not to direct vagal stimulation (*a*) Of the 15 patients, all except 2 (cases 4 and 7) complained of attacks of spontaneous dizziness and fainting, and in all 13 cases these, and severer symptoms, were induced with regularity by pressure on the carotid sinus Furthermore, the patients, without exception, stated that the nature of the spontaneous fainting, including the character of the aura, was identical with the manifestations of the induced attack (*b*) In 4 cases, turning the head in a certain direction induced dizziness and fainting In 1 of these cases, in which a metastatic carcinomatous node pressed directly on the sinus, the changes in heart rate and arterial blood pressure followed regularly a turn of the head (*c*) Fainting and convulsions were induced by pressure on the sinus, whereas complete compression of the common carotid artery and firm pressure on the vagus trunk just below the sinus failed to induce the symptoms and the characteristic changes in the cardiovascular system Compression of the carotid artery below the sinus with pressure on the vagus trunk resulted, on the contrary, in a moderate elevation of the heart rate (fig 21) and blood pressure, presumably because of the lowered intrasinal pressure In the presence of aneurysm of the sinus, slight localized touching of the skin over the median portion of the aneurysm resulted in a slowing of the heart and a fall in the blood pressure Such a gentle and superficial manipulation at an appreciable distance from the vagus could not stimulate this nerve directly (*d*) Unilateral novocainization of the sinus abolished the reaction ipsolaterally, but pressure on the opposite sinus continued to elicit a response Similarly, cutting the intercarotid nerve, in one case, resulted in complete recovery of the patient and abolition of the reaction (*e*) Novocainization of the vagus trunk below the sinus did not abolish the reaction of the ipsolateral sinus In 1 case mechanical stimulation of the vagus exposed surgically failed to induce the typical reaction (*f*)

Minute amounts of atropine administered centrally into the internal carotid artery abolished the reflex ipsolaterally but not contralaterally

The question now naturally arises whether cardiac slowing is ever caused by mechanical stimulation of the vagus in man This question can not yet be answered with absolute certainty, but the bulk of evidence to be enumerated strongly suggests that cardiac slowing practically never, or rarely, occurs from mechanical pressure over the unexposed vagi In animals, Hering (25) has found the vagi comparatively inexcitable to mechanical stimulation He pointed out that pressure applied over the vagus just below the sinus, with occlu-

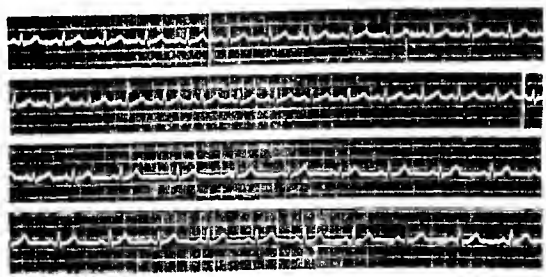


FIG 21 Case 14 Electrocardiogram Lead I *A*, *B*, *C* and *D* represent continuous tracing Vertical white lines in *A* and *B* indicate beginning and end of pressure on the right carotid artery *below* the sinus Note the slight speeding of the pulse following beginning of pressure, and the slowing following the end of pressure

sion of the carotid artery, produces tachycardia and vascular constriction as a result of fall in pressure within the sinus In man, both in health and in disease, pressure below the sinus, however firm, has seldom in our experience resulted in cardiac slowing or fall in blood pressure In the very rare instances in which temporary bradycardia has been observed by some, we believe that it probably resulted from traction on the sinus Sollmann and Brown (26) have shown that the caudal traction upon the central end of the divided carotid artery induces bradycardia in animals It is significant that in none of our cases with hyperactive sinus reflex did we observe cardiac slowing when pressing firmly against the vagus or the carotid artery If

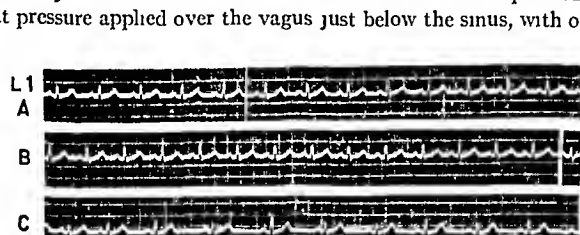
III DISCUSSION

A The evidence that the clinical manifestations are due to a hypersensitive carotid sinus reflex and not to direct vagal stimulation

The following evidence supports definitely the belief that the clinical manifestations presented are due to overactive carotid sinus reflex and not to direct vagal stimulation (*a*) Of the 15 patients, all except 2 (cases 4 and 7) complained of attacks of spontaneous dizziness and fainting, and in all 13 cases these, and severer symptoms, were induced with regularity by pressure on the carotid sinus Furthermore, the patients, without exception, stated that the nature of the spontaneous fainting, including the character of the aura, was identical with the manifestations of the induced attack (*b*) In 4 cases, turning the head in a certain direction induced dizziness and fainting In 1 of these cases, in which a metastatic carcinomatous node pressed directly on the sinus, the changes in heart rate and arterial blood pressure followed regularly a turn of the head (*c*) Fainting and convulsions were induced by pressure on the sinus, whereas complete compression of the common carotid artery and firm pressure on the vagus trunk just below the sinus failed to induce the symptoms and the characteristic changes in the cardiovascular system Compression of the carotid artery below the sinus with pressure on the vagus trunk resulted, on the contrary, in a moderate elevation of the heart rate (fig 21) and blood pressure, presumably because of the lowered intrasinal pressure In the presence of aneurysm of the sinus, slight localized touching of the skin over the median portion of the aneurysm resulted in a slowing of the heart and a fall in the blood pressure Such a gentle and superficial manipulation at an appreciable distance from the vagus could not stimulate this nerve directly (*d*) Unilateral novocainization of the sinus abolished the reaction ipsolaterally, but pressure on the opposite sinus continued to elicit a response Similarly, cutting the intercarotid nerve, in one case, resulted in complete recovery of the patient and abolition of the reaction (*e*) Novocainization of the vagus trunk below the sinus did not abolish the reaction of the ipsolateral sinus In 1 case mechanical stimulation of the vagus exposed surgically failed to induce the typical reaction (*f*)

Minute amounts of atropine administered centrally into the internal carotid artery abolished the reflex ipsolaterally but not contralaterally

The question now naturally arises whether cardiac slowing is ever caused by mechanical stimulation of the vagus in man This question can not yet be answered with absolute certainty, but the bulk of evidence to be enumerated strongly suggests that cardiac slowing practically never, or rarely, occurs from mechanical pressure over the unexposed vagi In animals, Hering (25) has found the vagi comparatively inexcitable to mechanical stimulation He pointed out that pressure applied over the vagus just below the sinus, with occlu-



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the manifestations were due to primary or associated hypersensitivity of the vagus, bradycardia would have been prone to develop in these cases

A few observations on the mechanical stimulation of the exposed vagus trunks in man are available Iacobovici, Nitzescu and Pop (27) found in 1 case that stimulation of the peripheral end of the divided vagus was without effect, while stimulation of the central end resulted in cardiac slowing They concluded, therefore, that the cardiac slowing was the result of a reflex rather than of direct stimulation They rightly emphasized, however, that the degree of pressure necessary to induce cardiac slowing was far in excess of that applied clinically in the "vagus pressure" tests Hill (28) stimulated mechanically, with the aid of dissecting forceps, both the carotid sinus and the vagus in 20 cases operated upon for carcinomas and other lesions of the neck This study is of limited value, however, because a general anesthetic was used Of 13 cases under ether anesthesia, none showed any response to sinus stimulation, and only 1 responded to vagal stimulation Two cases under chloroform yielded responses to sinus stimulation, and 1 to vagal stimulation Of 5 cases under gas and oxygen, 3 gave responses to sinus or to vagal stimulation, or to both We observed the effect of direct stimulation of the exposed vagus in 2 cases with hyperactive sinus, and found that slowing of the heart rate occurred in 1 case but not in the other It is obvious that local pinching of a nerve trunk with a metal instrument is not comparable with the technique of the clinical vagus test It has been indicated (29) that the cardiac slowing induced by digitalis is due in part to a reflex rather than to local stimulation of the vagus endings Thus motor stimulation of the vagus depends, at least in the majority of instances, on reflex stimulation

Cases with responses such as those described in this communication are not observed frequently, and they represent only a very small percentage of patients who suffer from fainting The cases studied have been gathered from a large amount of clinical material over a period of 3 years Our studies indicate that fainting observed in the patients with sensitive carotid sinus reflex has no relation to postural hypotension. None of the cases studied exhibited postural hypotension, and contrariwise 3 cases, not reported here, with pronounced

postural hypotension and fainting on standing, failed to show any symptoms or changes in the cardiovascular system following pressure on the carotid sinus

A search through the literature for evidence that convulsions and fainting may result from an overactive carotid sinus reflex revealed the following information Czermak (3) in his short but important communication in 1866, reporting observations on himself, mentions that pressure over the left side of his neck produced but transient slowing of his heart rate, while pressure over the right side caused more persistent cardiac slowing and sensations of vertigo and faintness He also remarked that over the right side, where the presssure induced this maximal effect, he palpated a small nodule next to the bulbous dilatation of the artery On the left side no such nodule was felt Czermak did not mention whether he suffered from spontaneous fainting One of the cases that we observed seems very similar but the responses were much more intense and the removal of the node and section of the intercarotid nerve stopped the seizures at once

Roskam (30) in 1930 reported the case of a man who had a carotid sinus so sensitive that the slightest pressure over it would precipitate syncope and violent convulsions Shaving over that area, or putting on a tight collar, would bring on the seizure This case is somewhat similar to case 15 observed by us Nathanson (31) has reported recently electrocardiographic and pharmacologic observations on a man 70 years of age, in whom slight compression of the right carotid sinus repeatedly elicited a cardiac standstill of 7 to 9 seconds' duration The subject suffered from mild anginal attacks, but no statement is made as to whether he ever suffered from spontaneous fainting attacks The cardiac standstill was abolished by epinephrin and atropine Ephedrine calcium gluconate and caffeine had no significant effect Other cases must have been observed, for clinicians of the past warned against pressure "on the vagus" Until recently, however, no correlation has been made between symptoms and the circulatory mechanism

B Types of cardiovascular responses

In the patients with fainting and convulsions, three main types of cardiovascular reaction were associated with the symptoms and signs

resulting from pressure on the carotid sinus (*a*) marked asystole or sudden slowing of the pulse, with or without marked fall in the arterial pressure, (*b*) marked fall in the blood pressure without essential cardiac slowing, (*c*) marked paling of the face followed by intense flush but without essential slowing of the heart rate and without fall in the arterial blood pressure Combinations of these types also existed

The explanation of the fainting and convulsions on the basis of cerebral ischemia in the first two groups with very slow heart rate and sudden fall in arterial pressure seems obvious The fainting and convulsions in the third group are rather remarkable and of special importance, as these cases showed no striking changes in the heart or in the general circulation In view of the fact that observations by Heymans (7) suggest a special connection between stimulation of the carotid sinus and changes in cerebral vessels in animals, that the patients studied by us exhibited constriction of the facial vessels, as indicated by pallor without fall in the systemic blood pressure, and that previous studies have demonstrated a close relation between the responses of the facial and the cerebral blood vessels (22), one can justifiably assume that in this third group of cases the fainting is produced by sudden changes in the cerebral vessels as a result of stimulation of the carotid sinus The character of the vascular change is probably constriction, followed by dilatation of the cerebral vessels

Thus, as far as the efferent portion of the carotid sinus reflex is concerned, the vagus nerves of the heart and the vasomotor nerves of the splanchnic and cerebral blood vessels represent the three main efferent cardiovascular nerve pathways of the reflex That the systemic hemodynamics have an important bearing on the fainting is shown also by the more prompt appearance of fainting while the patient was standing than when he was in the recumbent position Patients who at times did not faint while lying down, did so when standing

Following stimulation of the sinus, the factors which determine the predominant changes in the heart or in the splanchnic or cerebral vascular area are not entirely clear, although it appears that the sensitivity of the vascular areas of organs involved has an important bearing Patients with marked cardiac slowing were elderly persons usually with some degree of coronary arterial disease Hering (6)

and Heymans (7) attribute hypersensitivity of the carotid sinus reflex to local pathology in the sinus Danielopolu (32) believes that such a reflex is due to an abnormal state of the organs giving the marked response The patients who exhibited primarily a fall in blood pressure showed some degree of arterial hypertension The patients with fainting but without changes in the heart or peripheral vascular system were suffering from unstable central vasomotor system with psychologic responses of a neurosis Accordingly, in the hyperactive state of the reflex, the condition of the efferent end-organs as well as of the afferent end-organ—*i e*, the morphologic condition of the sinus—plays an important role Such a state of affairs is not unique with the carotid sinus reflex alone, for it exists in other pathologic reflexes That the hyperactive carotid reflex is not always caused by organic changes in the sinus or end-organs is shown by the behavior of young patients who exhibited temporary hyperactivity with fainting In 1 patient who returned to the hospital ward several times, the sensitivity of the reflex appeared to have some relation to the menstrual cycles

The effect of epinephrin in temporarily abolishing the symptoms and signs associated with any of the three types of cardiovascular reaction was to be expected, for epinephrin increases the cardiac output considerably, it stimulates the accelerator nerves and hence counteracts vagus stimulation, and in addition it has a direct constrictor effect on the vascular system including the vessels of the human brain (33) Each of these epinephrin effects would result in an absolute or a relative increase in blood flow through the brain Atropine, on the other hand, abolished fainting only in those cases in which this depended on asystole or slow cardiac rate from reflex vagus stimulation The fact that the fainting and convulsions due to a primary fall in the blood pressure, or to an assumed primary cerebral vascular change, were not prevented, indicates that in these vascular areas the responses set up by sinus stimulation travel in the sympathetic rather than in the parasympathetic channels This is of interest for it is known that certain vasodilator mechanisms, such as are stimulated by acetylcholine, are abolished by atropine (34)

The finding that the intracarotid administration of atropine in amounts so small as to have no systemic effect abolished the response of the reflex ipsolaterally, but not contralaterally, is of significance

It indicates that at least some of the central synapses of the reflex can be interrupted by the action of atropine The observations also demonstrate definitely that atropine has a central action, and under conditions described such a central action in man can be separated from the peripheral action These findings, as well as observations on the effects of the intracarotid administration of histamine and acetylcholine, indicate that substances injected into the internal carotid artery exert an action mainly on the same side of the brain—apparently the cross current of the cerebral circulation in man, if both carotids are patent, is not significant

The cerebral dilatation induced by histamine, acetylcholine or carbon dioxide failed to influence the attacks of syncope in any of the three types of cases The fact that, in cases without cardiac slowing and fall in blood pressure, pallor of the face followed instantaneously the pressure on the sinus, indicated that the constrictor effect of the efferent vasomotor nerve impulses set up by the stimulated sinus was a more powerful antagonist of the chemically induced vasodilatation

C Changes in the intracardiac conduction and rhythm

The electrocardiographic studies demonstrated in an impressive manner the intense intracardiac derangement that may result in man reflexly Such changes as complete asystole were induced reflexly Similarly premature beats and varying degrees of block between the auricles and ventricles have been observed There also developed changes in the ventricular complexes and in the character of the T wave. In one instance temporary auricular fibrillation followed unilateral section of the intercarotid nerve The most frequent findings were characterized by impairment of the conduction and of the cardiac functions These changes, however, are not the only effects of the carotid sinus reflex on the human heart We have observed in other instances, not reported here, instantaneous disappearance of auricular or ventricular paroxysmal tachycardias, or temporary changes of nodal rhythm to sinus rhythm. Freundlich (35) has recently reported 2 cases with circulatory failure in which the bundle branch block disappeared temporarily while pressure was applied, and later, with general improvement of the circulation, disappeared permanently. These observations demonstrate what a marked degree

of functional alteration may occur in the intracardiac conduction and cardiac function, furthermore, and this is quite remarkable, they show that these deep-seated changes can be induced reflexly through afferent stimulation of brain centers That cardiac arrhythmias in man can also occur from direct stimulation of brain centers is demonstrated by the temporary arrhythmias observed by us following fracture of the skull and cerebral injuries (36)

The fact that atropine abolished the appearance of all types of cardiac irregularities and disturbances in the intracardiac conduction induced by stimulation of the sinus indicates that these cardiac reflex changes were induced through alteration in the vagal tone Observations, by De Graff and Weiss (37), of cases with complete heart block indicate that the direct vagus control in man involves mainly the auricles, and that the vagi have but slight direct influence over the ventricles As far as the coronary blood vessels are concerned, these receive innervation through the coronary plexus from the vagi as well as from the accelerator nerves (38) The changes observed through sinus stimulation must depend, therefore, on the combined functional effect on the vagus, the auricles, and the coronary blood vessels Milder reflex stimulation of the vagi, particularly in tachycardia and bundle branch block, influences the auricular conduction system and the coronary circulation in such a manner that improvement in the cardiac nourishment and function or complete return to normal mechanism takes place In the presence of hyperactive reflex, on the other hand, powerful stimulation of the vagus results in apparently the opposite effect, namely, severe disturbance of the cardiac function Thus the basis of an "amphotropic" action of the sinus nerve lies not in the difference in action or mechanisms, but rather in the difference in intensity of the reflex, as well as in the state of nerve structure, conductive system and coronary vessels of the heart

D Adams-Stokes syndrome of reflex origin

The repeatedly induced A-V block with fainting and convulsions after stimulation of the sinus definitely establishes a neurogenic type of Adams-Stokes syndrome The theory that the vagus is responsible for the Adams-Stokes syndrome was first suggested by Charcot (39), following the classical demonstration of the inhibitory effect of the

vagus on the heart by the celebrated Weber brothers in 1850. With the discovery of the conductive system of the heart in the beginning of the present century, however, primary structural and functional changes within this system were held to be responsible for the syndrome (40) As such anatomic lesions were actually found postmortem in a number of cases of complete heart block, and as cases of vagus origin, on the other hand, were not demonstrated with the aid of precise measurements, the organic theory has become strengthened, and the nervous theory has gradually faded Although in the cases reported by Hay (41), Lutembacher (42), Gallemaerts (43), Starling (44), Flaum and Klima (45), the rôle of the vagus in precipitating Adams-Stokes attacks is suggestive or clear, the exact rôle of the nervous mechanism was not established In the cases studied by Flaum and Klima and in the one studied by Starling, we are dealing, apparently, with attacks of Adams-Stokes syndrome of vagovagal origin In the rare cases of complete block with Adams-Stokes syndrome observed by us (36), in which complete block developed rhythmically in association with Cheyne-Stokes breathing, we are probably dealing with another type of vagus reflex Lépine (46) reported a case in which compression of the pons and the medulla oblongata was held responsible In Boyd's case (47) luetic lesions of the fourth ventricle were considered etiologic Brissaud (48) claimed that the presence of gumma in the cerebellar peduncle and in Neuburger and Edinger's patient (cited in (45)) varix in the medulla was related to the Adams-Stokes attacks These case reports give suggestive evidence that in rare instances lesions of the medulla may precipitate Adams-Stokes attacks It seems probable, therefore, that just as in the cases of carotid sinus origin, so with the central and other nervous lesions it is always the overactive *reflex*, rather than local lesions of the vagus, that acts as a trigger in the precipitation of Adams-Stokes attacks

In practically all cases reported in the literature and observed by us, evidence of cardiac pathology, particularly of the sclerotic type, was present One may justifiably conclude, therefore, that if Adams-Stokes syndrome is caused by extracardiac nervous factors, this is usually a hyperactive reflex in which the cardiac efferent end-organs, and the afferent nerve endings in the sinus or the medullary centers

of the reflex alone or combined, are also diseased That the abnormal carotid sinus reflex and not the cardiac pathology played a dominant rôle in these cases is shown by the fact that complete block developed although no partial block preexisted, and contrariwise, in cases with unusually marked partial heart block, stimulation of the normal carotid sinus reflex failed to induce complete block or Adams-Stokes attacks (cf figs 2 and 3) Attention is also called to the fact that, on the basis of our observations, the fainting and convulsions in Adams-Stokes syndrome do not always depend solely on the temporary complete arrest of the chambers of the heart before the change in the rhythm At times the change in rhythm may be sudden and convulsions absent Fall in blood pressure as part of the carotid sinus reflex can play a predominant rôle in convulsions In some of our cases the convulsions came on after the block was established In another type of Adams-Stokes attacks the fainting and convulsions depend entirely on the relative slowing of the heart in complete block De Graff and Weiss (37) reported a case with permanent A-V block in which such attacks occurred whenever the heart rate fell to 12 or below per minute

E The cerebral circulation and convulsions

One of the original aims of study was to shed light on the interrelation between changes in the cardiovascular system and the occurrence of fainting and convulsions Satisfactory observations on this relationship are not available, mainly because syncope and convulsions usually develop unexpectedly, and they could not be induced with regularity The type of condition described, on the other hand, has lent itself ideally to such a study It has been shown that in association with complete asystole, fainting and convulsions developed regularly within 12 seconds with the body in the horizontal position The usual time required was 8 seconds In a number of instances, especially when the stimulus of pressure was more intense, the loss of consciousness was almost instantaneous and the convulsions occurred as early as 5 to 6 seconds It is probable that in these latter cases, in addition to changes in the systemic circulation, direct alterations in the cerebral blood vessels also played a rôle This contention is supported by the fact that syncope occurred as early as 8 seconds in cases with no essential fall in the arterial pressure and with no cardiac slowing

During the state of asystole there obviously existed a decreased blood flow through the brain Measurements of the cardiac output and velocity of blood flow also indicated that during the state of syncope and convulsions the systemic blood flow was distinctly diminished Similarly, the study of arterial and internal jugular blood indicated a decrease flow through the brain The observation that, as result of diminished sensitivity of the reflex, fainting and convulsions occurred in the upright position, but not in the horizontal position of the body, also indicates that cerebral ischemia played a significant rôle in the attacks On the other hand, the absolute values of the systemic or cerebral blood flow during fainting and convulsions were not outstandingly low They were certainly not lower than the values observed in the presence of heart disease without convulsions It is to be remembered, however, that the values for blood flow obtained represent average values during a period of 30 to 60 seconds The greatest decrease in the cerebral or systemic flow occurred very probably in the first part of the period when the stimulation was applied This conclusion is also supported by the observation that pallor of the face with or without cardiac slowing occurred immediately after the stimulation, and that often simultaneously with, or even before the onset of convulsions, an intense flush followed the pallor The cardiac slowing, likewise, was maximal immediately after the stimulation, and often by the time, or even before the convulsions set in, the heart rate increased considerably All these observations strongly suggest that in the development of syncope and convulsions, not so much the absolute degree of ischemia as *the time element of change from a normal state to an ischemic state plays a dominant rôle* Once this temporary but sudden ischemic state develops, a sequence of events is set up within the brain which then proceed independently to the development of convulsions, even if a hyperemia promptly follows the ischemia That the time element and the *relative* changes in the cerebral circulation play a dominant rôle in the development of other cerebral symptoms also has been demonstrated by one of us in studying the cerebral circulatory changes leading to headache It has been shown that sudden constriction as well as sudden dilatation of the cerebral blood vessels in man induces headache, but the same degree of vascular change induced slowly is

not associated with headache (33) Thus as with headache, so with fainting and convulsions, and probably with other cerebral symptoms and signs, it is not so much the absolute degree of alteration in the cerebral circulation as the rate (time element) of circulatory changes that plays a fundamental etiologic rôle Whether in addition to the cerebral circulation direct nerve stimuli from the sinus to the cerebral cells plays a rôle in the convulsions described is not known The 2 cases with periodic hyperactivity of the sinus suggest that chemical substances or psychic states may have an important bearing on convulsions In several instances with mild stimulation of the sinus we were able to prevent the attack by asking the patient questions in a loud tone

F The relation between convulsions due to hyperactive carotid sinus reflex and epilepsy

The connection between the carotid sinus and convulsions naturally raises the question of relationship between the carotid sinus and epilepsy in general If a close relationship existed, epilepsy would be approachable through surgical measures In 1 case with fainting and convulsions, such a surgical denervation of the carotid sinus did indeed result in complete recovery On the other hand, in 150 cases of epilepsy Lennox was unable to induce convulsions by pressure over either of the carotid sinuses (49) Danielopolu (50) in a recent communication claims that in the complicated vicious circle that leads to convulsions in epilepsy the carotid sinus reflex may be one of the many factors playing a rôle He suggests a complex operative procedure consisting in section of both carotid nerves, cervical sympathectomy, section of the vertebral nerves and of the communicating branches between the stellate ganglion and the vagus, and in addition section of the right vagus trunk below the recurrent laryngeal nerve As to the beneficial effect of such an operation, however, he offers no definite proof One must, therefore, caution against such procedure, lest false hopes may again be raised temporarily in this dread disease Our observations clearly demonstrated that the syndrome discussed by us is a specific one While convulsions and any reflex can be influenced to a *certain extent* by other reflexes, by chemical substances, and by psychic processes in general, we have emphasized that in the

cases studied, the other reflexes showed no abnormality, and contrariwise, in cases with postural hypotension the carotid sinus reflex was normal and had no relation to this condition We believe, therefore, that at present the evidence is such that section of the intercarotid nerve is indicated only in cases where the carotid sinus reflex is abnormal or where local disease of the sinus exists Before undertaking surgical procedures, the existence of such a state should be determined by study of the individual patient

G The carotid sinus and arterial hypertension

The experimental studies of Koch, Mies and Nordmann (51), Heymans (7), Wright, Kremer and Scarff (52) have demonstrated that following removal of the intercarotid and aortic nerves in animals chronic arterial hypertension develops In rabbits, in addition to the hypertension, degeneration and calcification of the media of the aorta and, to lesser extent, of other vessels develop As a result of these significant observations, and because of the powerful depressor effect of these nerves on the vascular bed, it has been suggested in the past that the insufficient or absent function of the intercarotid nerve may be responsible for the development of arterial hypertension in man Hering (6) was the first to suggest that atheromatous changes in the media and adventitia of the aorta and sinuses may interfere with transmission of the intravascular pressure to the sensory nerve endings Under such conditions the nerve endings may continue to respond to direct external mechanical stimulation, and yet endosinal pressure changes would result in but slight or no reflex response That atheromatous changes in the sinus are not necessarily associated with degeneration of the nerve endings has been shown by the careful histologic studies of Sunder-Plassmann (10) Hasselbach (53) studied the interrelation between structural changes in the sinus and arterial hypertension in man In 72 cases with 19 instances of probable hypertension he failed to observe a correlation between the degree of structural change in the sinus and the level of blood pressure Recently Keele (54) has reinvestigated this problem in 55 consecutive cases that came to postmortem examination. The age incidence of the series varied from 7 to 79 years A study was made of the gross structural condition of the arch of the aorta, the bifurcation of the

innominate, common carotid and common iliac arteries, and special attention was paid to the carotid sinuses In 20 cases histologic examination of the sinuses was made Five of these cases had shown marked hypertension during life and 3 additional cases exhibited enlarged hearts without valvular disease and with normal blood pressure before death Keele failed to observe a relationship between the degree of degenerative change in the sinuses and the aorta and the level of the blood pressure. He observed that atheromatous lesion of the carotid sinus is common, and is mainly related to age. Changes in the sinus were usually associated with similar degree of change in the aortic arch, the innominate and common iliac bifurcations, and the upper end of the common carotid artery On clinical examination of the structural characteristics of the sinuses we have frequently observed extensive calcification of the sinuses with normal blood pressure, and contrariwise, patients with various types of arterial hypertension frequently exhibited soft and normal sinuses The evidence available at present does not favor the belief that local pathology of the sinus bears an important rôle in the causation of arterial hypertension in man.

H The carotid sinus reflex and other vasodepressor mechanisms

Whether the carotid sinus nerve and the depressor aortic nerves represent a functional entity, so far as an afferent vasodepressor mechanism is concerned, or whether they are but part of a more extensive afferent vasodepressor mechanism, can not at present be stated with any degree of certainty Some clinical and experimental observations on arteriovenous fistulas and aneurysms located in various parts of the body strongly suggest the existence of such a widespread afferent vasodepressor system, at least potentially present in health, and actively present under pathologic conditions (55) Furthermore, the efferent paths of the carotid sinus reflex are often activated not only by the afferent impulses set up within the sinus, but also by afferent impulses of other medullary reflexes The following facts support such a contention

It was pointed out that the intercarotid nerve joins the glossopharyngeal nerve and often forms a communication with the vagus nerve also Thus the afferent impulses from the carotid sinus reach

each of the sinuses induced dizziness and fainting together with convulsive seizures On mild stimulation the convulsive seizures developed contralaterally A certain degree of quantitative correlation existed between the degree and duration of the pressure and the intensity of bodily response In 4 cases a sudden turn of the head induced dizziness and fainting

5 In 6 of the 15 cases there was aneurysmal dilatation of one or both sinuses, in 3 cases a small tumor pressing on the sinus was found, and in the remaining 6 cases no gross abnormality was detected These morphologic changes bear directly on the hyperactive state of the reflex, but they are not the sole underlying cause of such hyperactivity, as cases with similar changes but without hyperactivity of the sinus were observed

6 The hyperactivity of the sinus is usually permanent, but in 2 cases it was recurrent

7 Three main types of cardiovascular response were observed following stimulation of the sinus (*a*) marked asystole or sudden slowing of the heart rate, with or without marked fall in the arterial blood pressure, (*b*) marked fall in the arterial blood pressure, without essential cardiac slowing, and (*c*) changes in the cerebral circulation, without essential slowing of the heart rate and without fall in the arterial blood pressure

8 A hyperactive carotid sinus reflex can induce striking changes in the intracardiac conductive system Partial and complete heart block, temporary asystoles of the ventricle with continued auricular contraction, nodal rhythm, ventricular extrasystoles, changes in the shape of the T waves and complete inversion of the electrical axis in the heart were induced through the reflex stimulation of the heart

9 An explanation for the "amphotropic" effect of the carotid sinus reflex on the heart is offered

10 The observations presented demonstrate that Adams-Stokes syndrome can be induced reflexly by stimulation of the hyperactive carotid sinus reflex In the precipitation of such attacks, local abnormality of the heart also plays a rôle

11 During stimulation of the hyperactive carotid sinus reflex, the volume and velocity of the blood flow become decreased There is also a slowing of the blood flow through the brain, as indicated by blood gas studies

12 Epinephrin abolishes the cardiovascular responses and the symptoms of the hyperactive reflex Paralysis of the parasympathetic nerve endings with atropine abolishes the cardiac but not the peripheral vascular changes Amounts of atropine which are without systemic effect can abolish the ipsolateral reflex when injected into the internal carotid artery, the contralateral carotid sinus reflex remains unaltered Local anesthesia of the sinus also abolishes the ipsolateral but not the contralateral reflex The central or systemic administration of cerebral vasodilator substances has no appreciable effect on the reflex That the carotid sinus reflex is a deep-rooted central function is shown by the fact that it is unaffected by depression of the central nervous system with luminal

13 In 1 case, section of the intercarotid nerve abolished the spontaneous fainting attacks In this case temporary arterial hypertension of 2 days' duration, with temporary auricular fibrillation, followed the section of the nerve

14 Evidence is presented that the clinical symptoms and signs observed, as well as the clinical changes, are due to stimulation of the sinus and not to direct motor vagal stimulation In the majority of instances motor stimulation of the vagus in man is of reflex origin, rather than the result of direct stimulation of the motor vagus nerve

15 Cases with aura, dizziness, fainting and convulsions caused by hyperactive carotid sinus reflex afford an opportunity to study the relationship between the systemic and cerebral circulation and these manifestations Observations presented indicate that the rate (time element) rather than the absolute deviation from the normal circulatory state of the brain plays the primary rôle in the precipitation of fainting and convulsions A temporary sudden ischemia of even short duration sets up a sequence of events in the brain which then proceed independently to convulsions, even if a hyperemia promptly follows the ischemia

16 Pharmacologic observations indicate that the substances entering the human brain through one internal carotid artery supply mainly the ipsolateral hemisphere, there is no appreciable cross circulation between the two hemispheres under normal conditions

17 While convulsions can be caused by a hyperactive carotid sinus reflex, this type of response apparently plays no significant rôle in idiopathic epilepsy

18. Section of the carotid sinus nerve is advocated only in cases where specific hyperactivity of the carotid sinus reflex exists

19 The relation of the hyperactive carotid sinus reflex to other vasodepressor mechanisms in man is discussed, and an explanation for the different types of bodily response to carotid sinus stimulation is offered

We wish to express thanks to Drs Stanley Cobb and William G Lennox, for permission to study case 13 which we observed in 1929, to Drs Maurice and Frank Fremont-Smith, with whom we observed case 12; and to Dr Walter Burrage, who kindly referred to us case 15 We are also indebted to Miss Rose Shore and Mr Cecil Goodwin for technical assistance

V. SUMMARY OF CASES

Case 1 This patient, a 64-year-old Russian seaman, entered the hospital complaining that one day, while working on a ladder, he had fainted twice and fallen to the ground He recovered consciousness immediately, however, and felt perfectly well thereafter History was otherwise negative Physical examination showed moderately advanced, generalized arteriosclerosis and slight enlargement of the heart to the left Blood and urine were normal Blood pressure was 144/72 Kahn test was negative Electrocardiogram showed upward convexity of ST in Lead I Overlying the right carotid sinus was a small, firm, tumorous mass Pressure on this caused asystole, fall in blood pressure, fainting and convulsions

Case 2 This patient, a 64-year-old Irish wool inspector, entered the hospital complaining of having fainted and fallen to the ground the evening of admission He gave no history of previous syncope He had been without work for a year and had had poor food and lodgings Examination showed healed scars of pediculosis, skin lesions of pellagra, generalized arteriosclerosis, and an enlarged heart Blood findings were those of hypochromic anemia Urine was normal Blood pressure was 178/90 Kahn was positive Electrocardiogram showed inverted T in Lead I, with slight notching of R Both carotid sinuses were dilated and thickened and pressure on either one caused cardiac standstill, fall in blood pressure, fainting and convulsions

Case 3 This patient was a 71-year-old Irish plasterer While doing some light work around his house, he suddenly felt very dizzy and collapsed Consciousness was regained very quickly, but he felt weak and was brought to the hospital by ambulance There was no history of syncope previously Examination revealed generalized arteriosclerosis, slight cardiac enlargement, blood pressure 120/64 Blood and urine were normal Wassermann was negative There was a low take-off of the T wave in the electrocardiogram There was no demonstrable abnormality of the carotid sinuses, but pressure on either one caused slight slowing of the heart, marked fall in blood pressure, fainting and convulsions

Case 4 This patient, a 50-year-old colored laborer, gave a history of luetic infection and symptoms suggesting moderately advanced heart disease He had had no fainting attacks Examination revealed signs of aortic regurgitation and mild cardiac decompensation Blood and urine were normal Blood pressure was 140/0 Kahn was positive Electrocardiogram was normal Pressure on his left carotid sinus caused marked cardiac slowing, with upward convexity of ST in Lead I of the electrocardiogram, but no fall in blood pressure, and no fainting or convulsions

Case 5 This patient was a 62-year-old American laborer, who had been admitted to the hospital three times in the preceding 4 months, always with complaints of attacks of weakness and dizziness On the first admission, it was found that he had a lead line in his gums, and his attacks were therefore explained on the basis of lead encephalopathy Physical examination was otherwise negative, except for generalized arteriosclerosis Blood and urine were normal Blood pressure was 190/95 Kahn was negative He was given treatment designed to cause excretion of lead Later, when he returned, it was found that he had sclerosed carotid sinuses, pressure on the left of which caused asystole, fall in blood pressure, fainting and convulsions

Case 6 This patient was a 56-year-old male negro, who 5 years ago began having dyspnea on exertion as well as frequent dizzy spells which ended in unconsciousness for from 3 to 5 minutes This continued for 2 years "Blood test" then was positive, so he was given intravenous treatment which improved him a great deal One and one-half years ago the spells of dizziness returned He entered the hospital for these attacks Examination showed an enlarged heart, signs of aortic regurgitation and mild cardiac decompensation Blood and urine were normal Blood

pressure was 150/30 Kahn was positive Electrocardiogram was essentially normal The carotid sinus on the left was enlarged and overlaid by several soft glands Pressure on this sinus caused asystole, fainting and convulsions, but no fall in blood pressure

Case 7. This patient, a 59-year-old American salesman, gave a history of heart disease, cardiac decompensation and auricular fibrillation, for which he had been given large doses of digitalis He entered the hospital complaining of green vision Examination showed an enlarged heart, generalized arteriosclerosis, and auricular fibrillation Blood and urine were normal Blood pressure was 168/90 Kahn was negative Electrocardiogram showed auricular fibrillation, QRST complexes, normal Pressure on either carotid sinus caused complete A-V block, the ventricle took up a slower regular rhythm with complete change in QRST complexes

Case 8 This patient, a 21-year-old female of American birth, gave a history of fainting spells and nervousness for 3 months, not associated with catamenia, food, or anything of which she was aware Examination was essentially negative, and blood and urine were normal Kahn was negative Blood pressure was 114/66 Electrocardiogram was normal Pressure on the right carotid sinus caused pallor and fainting, but no slowing of pulse or fall in blood pressure This sensitivity disappeared while the patient was in the hospital, but returned temporarily about 2 months after her discharge

Case 9 This patient, a 14-year-old American boy, complained of fainting attacks 2 hours before admission He had had similar attacks between the ages of 1 and 4 years He had rheumatic fever at the age of 9 years Examination showed signs of mitral stenosis with a well-compensated heart Pressure on the right carotid sinus caused slowing of the heart, pallor, and dizziness, but no fall in blood pressure or unconsciousness

Case 10 This patient, a 56-year-old American male, had been discharged from the hospital about a month before the present admission At that time, he showed definite cardiac hypertrophy and hypertension He returned because of the inability to speak more than a few words He was able to read and write, and showed no mental confusion There was no evidence of motor impairment Physical examination revealed narrowing and tortuosity of the arteries of the ocular fundi, enlargement of the heart, and blood pressure 175/110 Blood and urine were normal

Kahn was negative There was no gross structural change evident in either carotid sinus, but pressure on either caused slowing of the pulse, fall in blood pressure, fainting and convulsions

Case 11 This patient, a 36-year old Irish housewife, first entered the hospital 8 years ago, at which time she had acute rheumatic fever She gave a history of another attack at the age of 10 In the past 8 years, she has had dyspnea on exertion, orthopnea, and infrequent fainting spells She always felt dizzy immediately before these attacks, and was always able to fall so as not to hurt herself Unconsciousness usually lasted about 10 to 15 minutes There have never been convulsive movements during the attacks, so far as she knows Physical examination showed slight cardiac enlargement and a presystolic rumble and thrill at the apex Blood and urine were normal Kahn was negative Pressure over the right carotid sinus caused very slight slowing of the heart, fall in blood pressure, pallor and fainting

Case 12 This was a man 74 years of age, who was seen in consultation by one of us (S W) on March 12, 1932 He gave a history of dizziness and fainting attacks for the preceding month and a half These attacks always came on when he was sitting or standing In some instances they were precipitated by turning his head to the right His past history revealed that he had had a growth on his right cheek and a gland in his right neck removed a year and a half previously Examination showed Argyll-Robertson pupils and Charcot knee (left) General examination otherwise was negative Blood Wassermann was negative, spinal fluid Wassermann strongly positive The right neck showed a scar from the operation, but no new palpable glands In the left neck, at the angle of the jaw, was a firm, non-tender mass about 2 cm in diameter Pressing this against the carotid artery caused marked slowing of the pulse, fall in blood pressure, and dizziness Pressure on the right carotid sinus brought on the same changes

Case 13 This patient, a 62 year old physician, was admitted to the hospital complaining of (*a*) mental fatigue and irritability of 3 years' duration, and (*b*) three spells of loss of consciousness during the past 3 years Each of the attacks came on after considerable physical and mental exertion They were not preceded by aurae or accompanied by convulsive movements There was a questionable past history of tuberculosis Examination showed a man well preserved both physically and mentally

(12) HEYMANS, C , AND BOUCKAERT, J -J Perfusion des sinus carotidiens isolés avec la pompe de Dale-Schuster Réflexes vasomoteurs, Compt rend Soc de biol 103 31, 1930

(13) SCHMIDT, C Carotid Sinus Reflexes to the Respiratory Center, Am J Physiol 102. 94, 1932

(14) KOCH, E Ueber den depressorischen Gefässreflex beim Karotisdruckversuche am Menschen, München med Wchnschr 71 704, 1924

(15) HESS, F O Über die Aetiologie des Hochdrucks und Blutdruckreaktionen, München med Wchnschr 72 709, 1925

(16) MEHRMANN, K Der Heringsche Karotisdruckversuch am Menschen, Inaug Diss , Bonn, 1925

(17) DANIELOPOLU, D , ASLAN, A , MARCU, I , PROCA, G -G , AND MANESCO, E Les zones réflexogènes carotidiennes, Presse méd 35 1585, 1927

(18) TOMANEK, Z Carotissinusreflex beim Menschen, Klin Wchnschr 7 898, 1928

(19) MANDELSTAMM, M , AND LIFSCHITZ, S Die Wirkung der Karotissinusreflexe auf den Blutdruck beim Menschen, Wien Arch f inn Med 22 321, 1932

(20) HAMILTON, W F , MOORE, J W , KINSMAN, J M , AND SPURLING, R G Studies on the Circulation, Am J Physiol 99 534, 1932

(21) WEISS, SOMA, AND LENNOX, W G The Cerebral Circulation XVII Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch Neurol and Psychiat 26 737, 1931

(22) WEISS, SOMA, ROBB, G P , AND ELLIS, L B The Systemic Effects of Histamine in Man, Arch Int Med 49 360, 1932

(23) ELLIS, L B , AND WEISS, SOMA A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-arterial Injection of Acetylcholine, J Pharmacol and Exper Therap 44: 235, 1932

(24) COBB, S , AND FREMONT-SMITH, F The Cerebral Circulation XVI Changes in the Human Retinal Circulation and in the Pressure of the Cerebrospinal Fluid during Inhalation of a Mixture of Carbon Dioxide and Oxygen, Arch Neurol and Psychiat 26 731, 1931

(25) HERING, H E Werden beim Vagusdruckversuch die herzhemmenden Vagusfasern direkt oder indirekt erregt? Verhandl d deutsch Gesellsch f inn Med 35 93, 1923

(26) SOLLMANN, T , AND BROWN, E D The Blood Pressure Fall Produced by Traction on the Carotid Artery, Am J Physiol 30 88, 1912

(27) IACOBOVICI, I , NITZESCU, I I , AND POP, A Experimentelle Untersuchungen uber die Physiologie der Carotisdrüse beim Menschen, Ztschr f d ges exper Med 66 359, 1929

(28) HILL, I G W Stimulation of the Vagus Nerve and Carotid Sinus in Man, Quart J Exper Physiol 22 79, 1932

(29) WEISS, SOMA The Effects of the Digitalis Bodies on the Nervous System An Analysis of the Mechanism of Cardiac Slowing, Nausea and Vomiting, Psychosis, and Visual Disturbance following Digitalis Therapy, Med Clin N Am 15 963, 1932

(30) ROSKAM, J Syncopes cardiaques graves et syncopes réflectées par hyperréflectivité sino-carotidienne, Presse méd 38 590, 1930

(31) NATHANSON, M H Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch Int Med 51 387, 1933

(32) Danielopolu, D , Marcou, I , and Proca, G G Sur la mécanisme de production des variations du réflexe sino-carotidien à l'état pathologique, Compt rend Soc de biol 109 767, 1932
(33) Weiss, Soma The Interaction between Emotional States and the Cardiovascular System in Health and Disease, Emanuel Libman Anniversary Volumes, 3 1181, International Press, New York, 1932
(34) Hunt, R Vasodilator Reactions, Am J Physiol 45 197, 1918
(35) Freundlich, J Ueber die Beeinflussung intraventrikulärer Leitungsstörung durch den Carotisdruck, Deutsch Arch f klin Med 168 360, 1930
(36) Weiss, Soma Unpublished Observations
(37) De Graff, A C , and Weiss, Soma Observations on the Extrinsic Nervous Control of the Auricles and Ventricles in Complete Auriculo Ventricular Block in Man, J Clin Investigation, 2 227, 1926
(38) Hochrein, M Der Koronarkreislauf, Julius Springer, Berlin, 1932
(39) Charcot, J M Leçons sur les maladies du système nerveux faites à la Salpêtrière Recueillies et publiées par Bourneville, A Delahaye, Paris, 1872–73
(40) Hannford, H Remarks on a Case of Gummata of the Heart, Death from Heart Block, Rhythmical Contraction of the Auricles during the Long Pauses, Brit M J 2 1745, 1904
(41) Hay, J Bradycardia and Cardiac Arhythmia Produced by Depression of Certain of the Functions of the Heart, Lancet 84 139, 1906
(42) Lutembacher, R Bradycardie orbostatique Intermittence de conduction du faisceau de His, Arch d mal du coeur 12 145, 1919
(43) Gallemaerts, V Dissociation auriculo-ventriculaire provoquée par l'orthostatisme (bradycardie orthostatique), Arch d mal du coeur 16 332, 1923
(44) Starling, H J Heart Block Influenced by the Vagus, Heart 8 31, 1921
(45) Flaum, E , and Klima, R Zur neurogenen Form des Adams Stokes'schen Symptomenkomplexes, Wien Arch f inn Med 23 223, 1932
(46) Lépine, R Sur un cas de syndrome d'Adams-Stokes sans blocage, Semaine méd , Paris, 27 601, 1907
(47) Boyd, quoted by C Kreisamper Ein kasuistischer Beitrag zur neurogenen Form des Adams-Stokes'schen Symptomenkomplexes, Zentralbl f Herz u Gefäss krankh 17 117, 1925
(48) Brissaud, E Leçons sur les maladies nerveuses Deuxième série, Masson et Cie , Paris, 1899
(49) Lennox, W G Personal Communications
(50) Danielopolu, D Sur la pathogénie de l'épilepsie et sur son traitement chirurgical, Presse méd 41 170, 1933
(51) Koch, E , Mies, H , and Nordmann, M Arterieller Hochdruck durch Dauerausschaltung der Blutdruckzügler, Ztschr f Kreislaufforsch 19 585, 1927
(52) Wright, Kremer, and Scarff Unpublished Observations, quoted by Keele (54)
(53) von Hasselbach, H Bestehen Beziehungen zwischen Veränderungen am Sinus caroticus und der Hypertonie? Beitr z path Anat u z allg Path 86 369, 1931
(54) Keele, C A Pathological Changes in the Carotid Sinus and their Relation to Hypertension, Quart J Med N S 2 213, 1933
(55) Ellis, L B , and Weiss, Soma The Local and Systemic Effects of Arteriovenous Fistula on the Circulation in Man, Am Heart J 5 635, 1930

(56) HATCHER, R A , AND WEISS, SOMA Studies on Vomiting, J Pharmacol and Exper Therap 22 139, 1923

(57) LEWIS, T Vasovagal Syncope and the Carotid Sinus Mechanism, Brit M J 1. 873, 1932

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